FILE 'REGISTRY' ENTERED AT 16:20:54 ON 05 MAR 2009
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DICTIONARY FILE UPDATES: 4 MAR 2009 HIGHEST RN 1115640-24-8

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TSCA INFORMATION NOW CURRENT THROUGH January 9, 2009.

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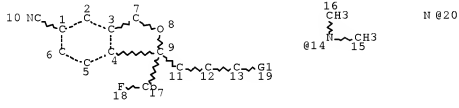
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

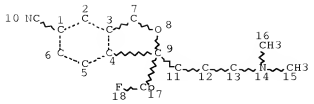
L1 STR



VAR G1=14/20
NODE ATTRIBUTES:
CONNECT IS X2 RC AT 11
CONNECT IS X2 RC AT 12
CONNECT IS X2 RC AT 13
CONNECT IS X1 RC AT 20
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 17
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L2 (125)SEA FILE=REGISTRY SSS FUL L1
L3 STR



Str. – Claim 1

NODE ATTRIBUTES:
CONNECT IS X2 RC AT 2
CONNECT IS X2 RC AT 5
CONNECT IS X2 RC AT 6
CONNECT IS X2 RC AT 7
CONNECT IS X3 RC AT 14
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 17
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE
L4 97 SEA FILE=REGISTRY SUB=L2 SSS FUL L3

100.0% PROCESSED 110 ITERATIONS 97 ANSWERS
SEARCH TIME: 00.00.01

FILE 'REGISTRY' ENTERED AT 16:07:44 ON 05 MAR 2009
E "3-CHLOROPROPYLAMINE"/CN 5
L5 3 S E3-5

FILE 'CAPLUS' ENTERED AT 16:22:52 ON 05 MAR 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 5 Mar 2009 VOL 150 ISS 10
FILE LAST UPDATED: 4 Mar 2009 (20090304/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2008.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate substance identification.

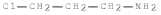
L6 461 SEA ABB=ON PLU=ON L5 OR 3(W)(CHLOROPROPYLAMINE OR (CL OR CHLORO)(W)(PROPYLAMINE OR (PROPYL OR PR)(W)AMINE) OR CHLOROPROPYL AMINE OR AMINOPROPYLCHLORIDE OR (AMINOPROPYL OR AMINO(W)(PR OR PROPYL))(W)(CL OR CHLORIDE))
L7 165 SEA ABB=ON PLU=ON L4/P
L8 6 SEA ABB=ON PLU=ON L6 AND L7

E1 THROUGH E12 ASSIGNED

L8 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1411354 CAPLUS Full-text
DOCUMENT NUMBER: 150:55903
TITLE: Attempted Resolution of Citalopram Using (-)-O,O'-Di-p-toluoyl-(R,R)-tartaric Acid, and Reflections on an Alkylation Reaction; Comment on an Article by Elati et al.
AUTHOR(S): Dancer, Robert James; de Diego, Heidi Lopez
CORPORATE SOURCE: Department for Process Research, H. Lundbeck A/S, Valby, DK-2500, Den.
SOURCE: Organic Process Research & Development (2009), 13(1), 23-33
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A recent article by Elati et al. (Elati, C. R.; Kolla, N.; Vankawala, P. J.; Gangula, S.; Chalamala, S.; Sundaram, V.; Bhattacharya, A.; Vurimidi, H.; Mathad, V. T. Organic Process Res. Dev.2007, 11, 289-292) describes the synthesis of escitalopram by means of a three-step process: (i) an alkylation reaction to provide didesmethylcitalopram, (ii) resolution of didesmethylcitalopram by classical resolution using (-)-O-O'-di-p-toluoyl-(R,R)-tartaric acid (DTT) as the chiral acid, and (iii) dimethylation of the resolved product to give escitalopram. However, they also mention resolution of citalopram itself by classical resolution, again using DTT as the chiral acid. We have been unable to reproduce their resolution of citalopram, obtaining only racemic or nearly racemic material. In order to better understand the system, we constructed two ternary solubility diagrams from solubility data at different temps. The resultant isotherms show the presence of a solid solution across the majority of the diagram in the temperature range 0-25°. This finding was in agreement with data from X-ray diffractograms. In addition, the solubility of the desired (S)-citalopram·DTT salt was found to be a factor of 5 higher than that of the corresponding R/S double addition salt. Furthermore, kinetics studies have indicated that the formation/crystal growth of the R/S double addition salt is preferred/faster than that of the desired (S)-citalopram·DTT salt. Taken as a whole, our findings show that resolution is not possible in any practical sense in the system described by Elati et al. Furthermore, we believe that detailed examination of their alkylation procedures casts doubt on their reproducibility.

IT 14753-26-5, 3-Chloropropylamine
RL: RCT (Reactant); RACT (Reactant or reagent)
(attempted resolution of citalopram using (-)-O,O'-Di-p-toluoyl-(R,R)-tartaric Acid, and attempted alkylation of cyanophthalane in acetone)
RN 14753-26-5 CAPLUS
CN 1-Propanamine, 3-chloro- (9CI) (CA INDEX NAME)

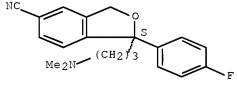


IT 928652-44-2P 1093185-94-4P 1093185-95-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(attempted resolution of citalopram using (-)-O,O'-Di-p-toluoyl-(R,R)-tartaric Acid, and attempted alkylation of cyanophthalane in acetone)
RN 928652-44-2 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2R,3R)-, compd. with (1S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (1:1) (CA INDEX NAME)

CM 1

CRN 128196-01-0
CMF C20 H21 F N2 O

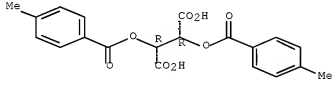
Absolute stereochemistry. Rotation (+).



CM 2

CRN 32634-66-5
CMF C20 H18 O8

Absolute stereochemistry. Rotation (-).

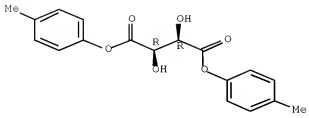


RN 1093185-94-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

CM 1

CRN 179340-01-3
CMF C18 H18 O6

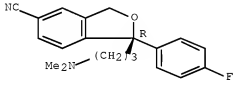
Absolute stereochemistry.



CM 2

CRN 128196-02-1
CMF C20 H21 F N2 O

Absolute stereochemistry. Rotation (-).

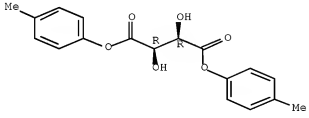


RN 1093185-95-5 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

CM 1

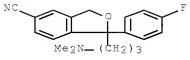
CRN 179340-01-3
CMF C18 H18 O6

Absolute stereochemistry.



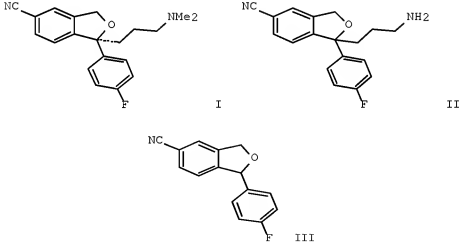
CM 2

CRN 59729-33-8
CMF C20 H21 F N2 O



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1411318 CAPLUS Full-text
DOCUMENT NUMBER: 150:55901
TITLE: Substrate Modification Approach to Achieve Efficient Resolution: Didesmethylcitalopram: A Key Intermediate for Escitalopram. Response to comments
AUTHOR(S): Elati, Chandrashekar R.; Kolla, Naveenkumar; Mathad, Vijayavitthal T.
CORPORATE SOURCE: Department of Research and Development, Dr. Reddy's Laboratories Ltd., Hyderabad, Andhrapradesh, 502325, India
SOURCE: Organic Process Research & Development (2009), 13(1), 34-37
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



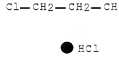
AB Recently, we published a synthesis of (S)-escitalopram (I) consisting of the resolution of didesmethylcitalopram (II) and subsequent methylation of S-didesmethylcitalopram. Some of our observations regarding citalopram resolution and C-alkylation of a benzofuran analog III to produce didesmethylcitalopram (II) were disputed by Dr. Dancer of H. Lundbeck

(preceding article). A detailed response to his comments regarding stabilization of the 3- chloropropylamine free base by dilution with certain solvents, its storage and handling, optimized exptl. conditions for C-alkylation to prepare didesmethylcitalopram, and a corrected process for citalopram resolution are included.

IT 6276-54-6, 3-Chloropropylamine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of didesmethylcitalopram via C-alkylation of benzofuran analog with 3-chloropropylamine free base)

RN 6276-54-6 CAPLUS

CN 1-Propanamine, 3-chloro-, hydrochloride (9CI) (CA INDEX NAME)



IT 1093186-97-0P
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(resolution of citalopram with (+)-di-p-toluoyltartaric acid)

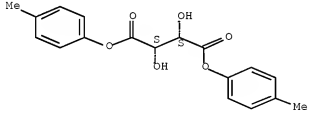
RN 1093186-97-0 CAPLUS

CN Butanedioic acid, 2,3-dihydroxy-, (2S,3S)-, 1,4-bis(4-methylphenyl) ester, compd. with (1S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (1:1) (CA INDEX NAME)

CM 1

CRN 943906-78-3
CMF C18 H18 O6

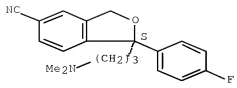
Absolute stereochemistry.



CM 2

CRN 128196-01-0
CMF C20 H21 F N2 O

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1293678 CAPLUS Full-text
DOCUMENT NUMBER: 149:493697
TITLE: Preparation of 2-aminopyrimidine-4-carbamates as inhibitors of Lck kinase enzyme
INVENTOR(S): Buchanan, John L.; Elbaum, Daniel; Martin, Matthew W.; McGowan, David C.; Novak, Perry M.; Nunes, Joseph J.
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: U.S., 93pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 7442698	B2	20081028	US 2004-891636	20040713
US 20050026914	A1	20050203		
AU 2004259737	A1	20050203	AU 2004-259737	20040715
CA 2532980	A1	20050203	CA 2004-2532980	20040715
WO 2005009978	A1	20050203	WO 2004-US23233	20040715
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1654238	A1	20060510	EP 2004-778640	20040715
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2007516212	T	20070621	JP 2006-521176	20040715
MX 2006000829	A	20060407	MX 2006-829	20060120
PRIORITY APPLN. INFO.:			US 2003-490220P P	20030724
			US 2004-891636 A	20040713
			WO 2004-US23233 W	20040715

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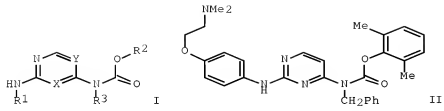
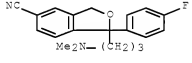


AB Title compds. represented by the formula I [wherein one of X and Y is N and the other of X an Y is CH; R1, R2, R3 = independently (un)substituted unsatd. monocycle, (un)saturated bicycle, (un)saturated heterocycle, etc.; and pharmaceutically acceptable salts thereof] were prepared as inhibitors of Lck kinase enzyme. For example, II was provided in a multi-step synthesis starting from th reaction of 2,4-dichloropyrimidine with benzylamine. I exhibited an average IC50 value of 1 uM or less in the human LCK HTFR assay for the inhibition of the Lck kinase enzyme. Thus, I and their pharmaceutical compns. are useful for the treatment of arthritis, rheumatoid arthritis, psoriatic arthritis, or osteoarthritis in a mammal comprising administering to the mammal a therapeutically-effective amount of a compound

IT 59729-33-8P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 2-aminopyrimidine-4-carbamates as inhibitors of Lck kinase enzyme)

RN 59729-33-8 CAPLUS

CN 5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER:	2007:412970 CAPLUS Full-text
DOCUMENT NUMBER:	148:262476
TITLE:	Process for the preparation citalopram
INVENTOR(S):	Kaushik, Vipin Kumar; Handa, Vijay Kumar; Sivakumaran, Meenakshi Sunderam
PATENT ASSIGNEE(S):	Aurobindo Pharma Limited, India
SOURCE:	Indian Pat. Appl., 11pp. CODEN: INXXBQ
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2005CH00036	A	20070316	IN 2005-CH36	20050118
PRIORITY APPLN. INFO.:			IN 2005-CH36	20050118

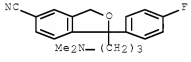
OTHER SOURCE(S): CASREACT 148:262476

AB The present invention relates to an industrially advantageous process for the preparation of highly pure citalopram and its pharmaceutical acceptable salts. Citalopram was prepared by addition of magnesium to 4-fluorobromobenzene, which was added to 5-cyanophthalide followed by alkylation with N,N-dimethyl-3-chloropropylamine to give 4-[4-(dimethylamino)propyl-1-(4-fluorophenyl)-1-hydroxybutyl]- 3-hydroxymethylbenzonitrile, which underwent cyclization to give citalopram, which was converted to its salts.

IT 59729-33-8P, Citalopram
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for the preparation citalopram)

RN 59729-33-8 CAPLUS

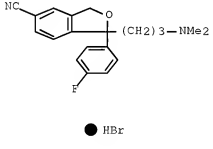
CN 5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



IT 59729-32-7P, Citalopram hydrobromide 207559-01-1P, Citalopram oxalate
RL: SPN (Synthetic preparation); PREP (Preparation)
(process for the preparation citalopram)

RN 59729-32-7 CAPLUS

CN 5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, hydrobromide (1:1) (CA INDEX NAME)



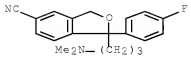
RN 207559-01-1 CAPLUS

CN 5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, ethanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 59729-33-8

CMF C20 H21 F N2 O



CM 2

CRN 144-62-7
CMF C2 H2 O4

L8 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:451372 CAPLUS Full-text
DOCUMENT NUMBER: 142:481937
TITLE: Preparation of enantiomerically enriched escitalopram
INVENTOR(S): Sundaram, Venkataraman; Mathad, Vijayavitthal Thippannachar; Venkavala, Pravinachandra Jayanthilal; Elati, Chandrashekar Ravirama; Kolla, Naveenkumar; Govindan, Shanmugam; Chalamala, Subrahmanyeshwara Rao; Gangula, Srinivas
PATENT ASSIGNEE(S): Reddy's Laboratories, Inc., USA; Reddy's Laboratories Ltd.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005047274	A1	20050526	WO 2004-US38490	20041112
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2004CH00370	A	20070223	IN 2004-CH370	20040422
CA 2575975	A1	20050526	CA 2004-2575975	20041112

EP 1706394 A1 20061004 EP 2004-811264 20041112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS
IN 2006CN02934 A 20070608 IN 2006-CN2934 20060809
US 20090018351 A1 20090115 US 2007-595794 20070130
PRIORITY APPLN. INFO.: IN 2003-CH924 A 20031112
IN 2004-CH370 A 20040422
US 2004-598725P P 20040804
WO 2004-US38490 W 20041112

OTHER SOURCE(S): CASREACT 142:481937

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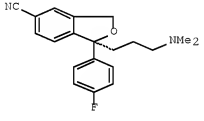
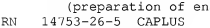


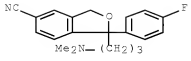
I

AB A process is disclosed for the preparation of enantiomerically enriched escitalopram. The process is comprised of: i. reacting 5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran with 3- chloropropylamine in the presence of a base; ii. reacting the product from (i) with an enantiomerically pure acid (e.g., (-)-di-p-toluoyltartaric acid); iii. hydrolysis of the resulting intermediate, and iv. methylation and recovery of escitalopram (I). The current process minimizes the production of undesired byproducts.

IT 14753-26-5, 3-Chloropropylamine
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of enantiomerically enriched escitalopram)
RN 14753-26-5 CAPLUS
CN 1-Propanamine, 3-chloro- (9CI) (CA INDEX NAME)

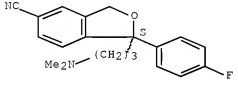


IT 59729-33-8P, 1-(3-(Dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile 128196-01-0P, (+)-(S)-1-(3-(Dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of enantiomerically enriched escitalopram)
RN 59729-33-8 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



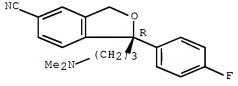
RN 128196-01-0 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, (1S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 128196-02-1P, (-)-(R)-1-(3-(Dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile
219861-08-2P, (+)-(S)-1-(3-(Dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of enantiomerically enriched escitalopram)
RN 128196-02-1 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, (1R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

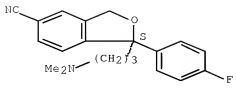


RN 219861-08-2 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, (1S)-, ethanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 128196-01-0
CMF C20 H21 F N2 O

Absolute stereochemistry. Rotation (+).



CM 2

CRN 144-62-7
CMF C2 H2 O4

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:99485 CAPLUS Full-text
DOCUMENT NUMBER: 142:198090
TITLE: Preparation of 2-aminopyrimidines and 2-aminopyridine-4-carbamates for use in the treatment of autoimmune diseases
INVENTOR(S): Buchanan, John L.; Elbaum, Daniel; Martin, Matthew W.; McGowan, David C.; Novak, Perry M.; Nunes, Joseph J.
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 267 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005009978	A1	20050203	WO 2004-US23233	20040715
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 7442698	B2	20081028	US 2004-891636	20040713
US 20050026914	A1	20050203		

AU 2004259737	A1	20050203	AU 2004-259737	20040715
CA 2532980	A1	20050203	CA 2004-2532980	20040715
EP 1654238	A1	20060510	EP 2004-778640	20040715
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JP 2007516212	T	20070621	JP 2006-521176	20040715
MX 2006000829	A	20060407	MX 2006-829	20060120
PRIORITY APPLN. INFO.:			US 2003-490220P	P 20030724
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OTHER SOURCE(S): CASREACT 142:198090; MARPAT 142:198090

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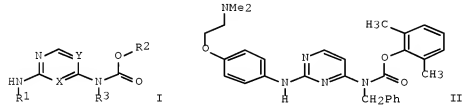


I II

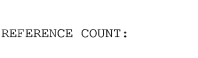
AB Pyrimidine or pyridine carbamates I [wherein X, Y = N or CH, provided that at least one of X and Y is CH; R1 - R3 = certain (un)substituted alkyl, monocyclic or bicyclic ring; or pharmaceutically acceptable salts thereof] were prepared For example, substitution of 2,4-dichloropyrimidine at the C4 with benzylamine followed by acylation of the resultant secondary amine with 2,6-Dimethylphenyl chloroformate, and subsequent amination at the C2 with 4-(2-dimethylaminoethoxy)phenylamine afforded II. Representative compds. I exhibited inhibition with IC50 values of ≤10 μM in the LCK-homogeneous time resolved fluorescent kinase assay and other assays. Therefore, I and pharmaceutical compns. thereof are active protein kinase inhibitors and T cell activation inhibitors, and are useful in the prophylaxis and treatment of many diseases such as autoimmune and hyperproliferative disorders.

IT 59729-33-8P

RL: SPN (Synthetic preparation); PREP (Preparation)
(Preparation of 2-aminopyrimidines and 2-aminopyridine-4-carbamates for use in the treatment of autoimmune diseases)

RN 59729-33-8 CAPLUS

CN 5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

FILE 'MEDLINE' ENTERED AT 16:23:08 ON 05 MAR 2009

FILE 'BIOSIS' ENTERED AT 16:23:08 ON 05 MAR 2009

FILE 'EMBASE' ENTERED AT 16:23:08 ON 05 MAR 2009

L9 16863 SEA ABB=ON PLU=ON L4
L10 5 SEA ABB=ON PLU=ON L9(L)(PREP? OR MANUF? OR PRODUCTION OR PRODUCING OR PRODUCE#)
L11 2 DUP REM L10 (3 DUPLICATES REMOVED)

L11 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2009066309 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 19137905
TITLE: Bioequivalence of two commercial preparations of escitalopram oxalate/clonazepam using a liquid chromatography-electrospray mass spectrometry method.
AUTHOR: Agarwal Sangita; Gowda Kadajji Veeran; Selvan Perumal Senthamil; Chattaraj Tapas Kumar; Pal Tapan Kumar
CORPORATE SOURCE: Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India.
SOURCE: Arzneimittel-Forschung, (2008) Vol. 58, No. 11, pp. 551-6.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(CLINICAL TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200902
ENTRY DATE: Entered STN: 14 Jan 2009
Last Updated on STN: 24 Feb 2009
Entered Medline: 23 Feb 2009

AB OBJECTIVE: A randomized, two-way crossover study was conducted in 24 fasting healthy male volunteers of Indian origin to compare the bioavailability of two brands of a fixed dose combination of escitalopram oxalate (CAS 219861-08-2) 10 mg and clonazepam (CAS 1622-61-3) 0.5 mg tablets, using Estomine-zee as test and a commercially available formulation as the reference product. The pharmacokinetics of escitalopram oxalate and clonazepam individually after oral administration of tablet formulation has been extensively evaluated in adult volunteers. However, no published data are available regarding the pharmacokinetics and bioavailability of this particular fixed dose combination. METHOD: The trial was designed as a randomized, balanced, open-label, 2-period cross-over study. The drug was administered with 240 ml of water after a 10-h overnight fasting on two treatment days separated by a 21-day washout period. After dosing, serial blood samples were collected for a period of 96 h. Plasma harvested from blood was analyzed by simple rapid, selective and validated liquid chromatography-electrospray mass spectrometry (LC-ESI-MS/ MS) using diazepam (CAS 439-14-5) as an internal standard. RESULTS: The calibration curves were found to be linear in the range of 1-25 ng/ml and 1-10 ng/ml for escitalopram oxalate and clonazepam, respectively, with a mean correlation coefficient of more than 0.99. No statistically significant differences were obtained between the two products with respect to the mean concentration-time profiles or in the pharmacokinetic parameters,

including the area under the serum concentration-time curve from the present study. CONCLUSION: Based on the statistical inferences, it was concluded that the test product is bioequivalent to the reference product. Both preparations were well tolerated with no adverse reactions throughout the study.

L11 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2006042076 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16430026
TITLE: Bioavailability investigation of two different oral formulations of citalopram, a so-called 'second generation' antidepressant drug.
AUTHOR: Gschwend Michael H; Richter Jutta; Sennewald Regina; Guserle Richard; Renner Jurgen; Martin Wolfgang
CORPORATE SOURCE: Pharmakin GmbH, Gesellschaft fur Pharmakokinetik, Ulm Germany.. michael.gschwend@pharmakin.de
SOURCE: Arzneimittel-Forschung, (2005) Vol. 55, No. 12, pp. 730-7.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
(CLINICAL TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200602
ENTRY DATE: Entered STN: 25 Jan 2006
Last Updated on STN: 28 Feb 2006
Entered Medline: 23 Feb 2006

AB Citalopram (CAS 59729-33-8) belongs to the so-called 'second generation' antidepressant drugs and is used for the treatment of patients with major depression or other depressive disorders. In the present study, two different oral citalopram formulations (Citalopram-ratiopharm film-coated tablets as test preparation and tablets of a reference preparation distributed in Germany) were investigated in 20 healthy volunteers in order to prove bioequivalence between both preparations. A single 40 mg oral dose was administered according to an open, randomised, two-period cross-over design in the fasted state. Blood samples for determination of citalopram plasma concentrations were collected at pre-defined time points up to 168 h following drug administration. A wash-out period of 21 days separated both treatment periods. Citalopram plasma concentrations were determined by means of a validated HPLC method with fluorescence detection. Maximum plasma concentrations (Cmax), of 34.77 ng/ml (test) and 34.42 ng/ml (reference) were achieved. Areas under the plasma concentration-time curve (AUC0-infinity) of 1,719.69 ng*h/ml (test) and 1,725.71 ng*h/ml (reference) were determined. The results showed nearly identical rate and extent of drug absorption. Also further pharmacokinetic parameters were well comparable with each other. Thus, tmax showed values of 3.29 h (test) and 3.77 h (reference). The plasma elimination half-life (t1/2) was 42.50 h (test) und 44.46 h (reference). Both primary target parameters Cmax and AUC0-infinity were tested parametrically by analysis of variance (ANOVA). Bioequivalence between test and reference preparation was demonstrated since for both parameters AUC and Cmax the 90 % confidence intervals of the T/R-ratios of logarithmically transformed data were in the generally accepted range of 80 %-125 %.

FILE CONTENT: 1961-PRESENT VOL 150 ISS 8 (20090227/ED)

MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

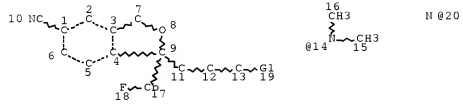
MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US 20090018200 15 JAN 2009
DE 102007040251 08 JAN 2009
EP 2014745 14 JAN 2009
JP 2009007348 15 JAN 2009
WO 2009012656 29 JAN 2009
GB 2450771 07 JAN 2009
FR 2918372 09 JAN 2009
RU 2342397 27 DEC 2008
CA 2631186 19 DEC 2008

Expanded G-group definition display now available.

The new MARPAT User Guide is now available at:
http://www.cas.org/support/stngen/stndoc/marpat.html.

L12 STR



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STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
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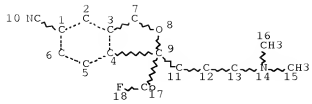

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NUMBER OF NODES IS  18

STEREO ATTRIBUTES: NONE

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L17          18 SEA FILE=MARPAT SUB=L14 SSS FUL L15 (MODIFIED ATTRIBUTES)

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SEARCH TIME: 00.00.01

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                                    RL-role; PREP/BMF/IMF/SPN/BPN-preparation/manufacture

     FILE 'MARPAT' ENTERED AT 16:28:08 ON 05 MAR 2009
L21          16 S L20

L21  ANSWER 1 OF 16  MARPAT  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        150:48135  MARPAT  Full-text
TITLE:                   Deuterium-enriched escitalopram for treatment of
                         mental disorders
INVENTOR(S):             Czarnik, Anthony
PATENT ASSIGNEE(S):      Protia LLC, USA
SOURCE:                  PCT Int. Appl., 36pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  2
PATENT INFORMATION:

     PATENT NO.       KIND  DATE           APPLICATION NO.  DATE
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WO 2008157271	A1	20081224	WO 2008-US66802	20080613

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 20080312318	A1	20081218	US 2007-762818	20070614

PRIORITY APPLN. INFO.: US 2007-762818 20070614

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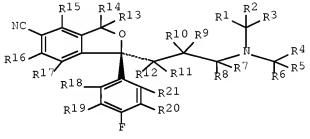

I

AB The present application describes deuterium-enriched escitalopram compds. I (R1-R21 = independently hydrogen or deuterium; wherein the abundance of deuterium in R1-R21 is at least 5%, with the proviso that if R1-R3 or R7-R8 are deuterium, then at least one other R is a deuterium), pharmaceutically acceptable salt forms thereof, and methods of treating major depressive disorder, generalized and social anxiety disorder, panic disorder, and/or obsessive compulsive disorder using the same.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 2 OF 16 MARPAT COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER:	147:211613 MARPAT Full-text
TITLE:	Process for asymmetric alkylation of carbonyl compounds
INVENTOR(S):	Albert, Martin; Sturm, Hubert; Berger, Andreas; Kremminger, Peter
PATENT ASSIGNEE(S):	Sandoz A.-G., Switz.
SOURCE:	PCT Int. Appl., 36pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007082771	A1	20070726	WO 2007-EP516	20070122
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AU 2007207103	A1	20070726	AU 2007-207103	20070122
CA 2636256	A1	20070726	CA 2007-2636256	20070122
EP 1966127	A1	20080910	EP 2007-702933	20070122
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MX 2008009383	A	20080805	MX 2008-9383	20080722
KR 2008090444	A	20081008	KR 2008-717910	20080722
PRIORITY APPLN. INFO.:			GB 2006-1286	20060123
			WO 2007-EP516	20070122

OTHER SOURCE(S): CASREACT 147:211613

AB This invention relates to a process for stereoselective alkylation of carbonyl groups comprising reaction of a carbonyl compound (containing an anchor group capable of reacting with a boric or boronic acid derivs.) with an organometallic compound in the presence of a chiral alc. and a boron compound For example, 4-(4-fluorobenzoyl)-3- (hydroxymethyl)benzonitrile was reacted with (1S,2S)-N-methylpseudoephedrine and diisopropoxymethylborane, followed by the addition of dimethylaminopropyl magnesium chloride to give (S)-4-[4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)benzonitrile with 90.0% enantiomeric excess. The chiral tertiary alc. obtained in the previous step is an useful intermediate for synthesizing antidepressant drug Escitalopram.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 16 MARPAT COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 146:358686 MARPAT Full-text

TITLE: Process for preparing tetrahydroisobenzofuran derivatives and their intermediates useful in the treatment of diseases

INVENTOR(S): Leone, Mario

PATENT ASSIGNEE(S): Icrom S.p.A., Italy

SOURCE: Ital. Appl., 25pp.
CODEN: ITXXCZ

DOCUMENT TYPE: Patent

LANGUAGE: Italian

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IT 2001MI1529	A1	20030120	IT 2001-MI1529	20010718
PRIORITY APPLN. INFO.:			IT 2001-MI1529	20010718

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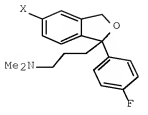


AB The invention relates to a process for preparing compds. of formula I and their intermediates. Compds. of formula I wherein X is halo, CF3, CN or acyl; and the process for preparing them are claimed. Example compound I (X = Br) was prepared from 5-bromophthalide, 4-fluorophenylmagnesium bromide and 3-dimethylamino-1-chloropropane using acid-mediated cyclization as the key step. These compds. may be useful as pharmaceutical compds.

L21 ANSWER 4 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 146:169401 MARPAT Full-text
TITLE: orodispersible tablets comprising crystalline base of escitalopram
INVENTOR(S): Dancer, Robert; Petersen, Hans; Nielsen, Ole; Rock, Michael Harold; Eliasen, Helle; Liljegren, Ken
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: U.S. Pat. Appl. Publ., 16pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070021499	A1	20070125	US 2006-425522	20060621
US 20080161388	A1	20080703	US 2008-46984	20080312
US 20080161584	A1	20080703	US 2008-46999	20080312
PRIORITY APPLN. INFO.:			US 2005-693214P	20050622
			US 2006-425522	20060621

AB The present invention relates to the crystalline base of the antidepressant, escitalopram, formulations of the base, a process for the preparation of purified salts of escitalopram, such as the oxalate, the salts obtained by the process and formulations containing such salts, and a process for the preparation of purified escitalopram free base or salts of escitalopram, such as the oxalate, using the hydrobromide, the salts obtained by the process and formulations containing such salts. Finally the present invention relates to an orodispersible tablet having a hardness of at least 22 N and an oral-disintegration time of <120 s and comprising an active pharmaceutical ingredient adsorbed onto a water soluble filler wherein the active pharmaceutical ingredient has a m.p. in the range of 40-100°, as well as a method for making such an orodispersible tablet. Thus, tablets contained fenofibrate 5.02, Peralitol SD200 136.46, Avicel PH102 25.02, AcDiSol 9.00, and Mg stearate 4.5 mg/tablet.

L21 ANSWER 5 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 146:87640 MARPAT Full-text
TITLE: Orodispersible tablets comprising crystalline escitalopram
INVENTOR(S): Dancer, Robert; Petersen, Hans; Nielsen, Ole; Rock, Michael Harold; Eliasen, Helle; Liljegren, Ken
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 48pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

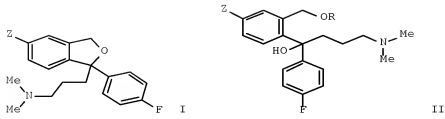
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006136169	A2	20061228	WO 2006-DK366	20060622
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2006261452	A1	20061228	AU 2006-261452	20060622
CA 2612827	A1	20061228	CA 2006-2612827	20060622
CA 2646780	A1	20061228	CA 2006-2646780	20060622
EP 1896439	A2	20080312	EP 2006-742481	20060622
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
GB 2442160	A	20080326	GB 2007-24557	20060622
DE 112006001619	T5	20080612	DE 2006-112006001619	20060622
HU 2008000135	A2	20080630	HU 2008-135	20060622
HU 2008000135	A3	20090128		
GB 2448834	A	20081029	GB 2008-11164	20060622
JP 2008546724	T	20081225	JP 2008-517323	20060622
CZ 299906	B6	20081229	CZ 2007-898	20060622
MX 2007015328	A	20080215	MX 2007-15328	20071205
CN 101189220	A	20080528	CN 2006-80020039	20071206
KR 2008018191	A	20080227	KR 2007-728918	20071211
BG 110024	A	20080530	BG 2007-110024	20071219
FI 20070107133	A	20071220	FI 2007-7133	20071220
IN 2007CN05887	A	20080613	IN 2007-CN5887	20071220
LV 13677	B	20080520	LV 2007-157	20071221
NO 2008000359	A	20080118	NO 2008-359	20080118
DK 2008000075	A	20080315	DK 2008-75	20080121
FI 2008000548	A	20081007	FI 2008-548	20081007
PRIORITY APPLN. INFO.:			DK 2005-912	20050622
			GB 2007-24557	20060622
			WO 2006-DK366	20060622
			CA 2009-2612827	20090116

AB The present invention relates to the crystalline base of the antidepressant drug, escitalopram, formulations of the base, a process for the preparation of purified salts of escitalopram, such as the oxalate and a process for the preparation of purified escitalopram free base or salts of escitalopram, such as the oxalate, using the hydrobromide, the salts obtained by the process and formulations containing such salts. Finally the present invention relates to an orodispersible tablet having a hardness of at least 22 N and an oral-disintegration time of <120 s and comprising an active pharmaceutical ingredient adsorbed onto a water soluble filler wherein the active pharmaceutical ingredient has a m.p. in the range 40-100°, as well as a method for making such an orodispersible tablet.

L21 ANSWER 6 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 144:274127 MARPAT Full-text
TITLE: Process for preparation of citalopram and its enantiomers via acid or base cyclization of the diol
INVENTOR(S): Periyandi, Nagarajan; Kilaru, Srinivasu; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006021971	A2	20060302	WO 2005-IN276	20050812
WO 2006021971	A3	20060713		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
IN 2004MU00912	A	20070420	IN 2004-MU912	20040823
EP 1797060	A2	20070620	EP 2005-815687	20050812
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
KR 2007083586	A	20070824	KR 2007-706600	20070322
US 20080177096	A1	20080724	US 2008-24492	20080201
PRIORITY APPLN. INFO.:			IN 2004-MU912	20040823
			WO 2005-IN276	20050812
			US 2007-660742	20070222

OTHER SOURCE(S): CASREACT 144:274127
GI



I II

AB The invention provides a process for preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile I (Z = CN; citalopram) and its enantiomers. The process for preparation of compound I comprising reacting a compound of formula II (R = H), in the presence of a base, with a compound of formula RX, wherein R is (un)substituted alkyl, (un)substituted alkenyl, and (un)substituted (hetero)aryl; X is from F, Cl, Br, I, CN, OTf and OR1; R1 is (un)substituted alkyl; Z is CN or a group that may be converted to a cyano group; so that an intermediate ether derivative, where R is as defined above, is formed from said reaction, which ether cyclizes to give a compound of formula I, where Z is not a cyano group, and conversion of the group Z in the compound of formula I to a cyano group to form racemic I (Z = CN), is claimed in this invention. The invention also provides ether compds., compds. of formula II and a process for preparation thereof. (S)-(+)-Citropram, i.e., (S)-(+)-I (Z = CN) was prepared by nucleophilic aromatic substitution of 2,5-dichloronitrobenzene with (S)-(-)-II (Z = CN; R = H) to give the corresponding benzylic Ph ether, that was converted to its HCl salt, and cyclized in the presence of potassium carbonate to give (S)-(+)-I.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 7 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 143:346931 MARPAT Full-text
TITLE: Process for the preparation of citalopram and its intermediates
INVENTOR(S): Ikemoto, Tetsuya; Watanabe, Yosuke
PATENT ASSIGNEE(S): Sumitomo Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 57 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2005263741	A	20050929	JP 2004-81592	20040319
WO 2005090290	A1	20050929	WO 2005-JP5466	20050317

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW,

AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2004-81592 20040319

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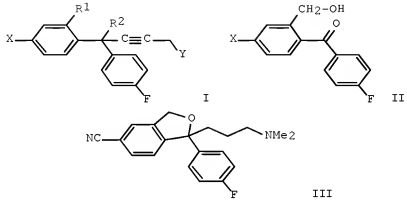

AB A process for the preparation of title compds. of formula I [R1 = CH2OH; R2 = OH; or R1R2 = -CH2O-; X = CN, CHO, halo, etc.; Y = dialkylamino, NO2, halo, etc.] comprising reacting a compound of formula II (X is defined as above) with a compound of formula M-C.tplbond.CCH2Y1 (M = Li, Na, MgCl, etc.; Y1 = dialkylamino, nitro or OR; R = (un)substituted heterocyclyl, alkyl, aralkyl or silyl) is disclosed. For example, reaction of II (X = CN) with LiC.tplbond.CCH2OTHP (73%), followed by intramol. cyclization, mesylation, substitution with dimethylamine, provided I [R1R2 = -CH2O-, X = CN, Y = NMe2], which was introduced to citalopram base III after redn (54%, 4 steps). This invention offered a production method for the preparation of citalopram, which is an important antidepressant.

L21 ANSWER 8 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 143:266808 MARPAT Full-text
TITLE: Process for producing optically active citalopram, intermediates therefor, and processes for producing these
INVENTOR(S): Ikemoto, Tetsuya; Watanabe, Yosuke
PATENT ASSIGNEE(S): Sumitomo Chemical Company, Limited, Japan
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005082842	A1	20050909	WO 2005-JP3815	20050228
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,				

MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW,
AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ,
DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC,
NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG
JP 2005247710 A 20050915 JP 2004-56917 20040301
PRIORITY APPLN. INFO.: JP 2004-56917 20040301
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A compound (I) (X = cyano or group convertible into cyano group), compound (II) [X = same as above; R1, R2 = (un)substituted lower alkyl; n = 0-3; * denotes an asym. carbon atom], compound (III) (X, R1, R2, n, * = same as above; Y1 = dimethylamino or group convertible into dimethylamino group) and compound (IV) (X, Y1 = same as above) are prepared by oxidation of 2-benzoylbenzyl alc. (V) (X = same as above), cyclic acetalization of the resulting I with optically active diol of formula R1C*H(OH)(CH2)nC*H(OH)R2 (R1, R2, n = same as above), addition reaction of the rersulting II with M(CH2)3Y1 (M = Li, MgX1; X1 = halogen atom), and deacetalization of the resulting III to give the benzaldehyde IV. Optically active citalopram (VI), which is known as an antidepressant, is prepared by reductive cyclization of IV to 1,3-dihydroisobenzofuran derivative (VII) (X, Y1 = same as above) and if necessary, conversion of the group X and Y1 into cyano and dimethylamino group, resp.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 9 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 140:181204 MARPAT Full-text
TITLE: Enzymic separation of intermediates for the preparation of escitalopram
INVENTOR(S): Taoka, Naoaki; Kato, Takahisa; Yamamoto, Shogo; Yoshida, Takashi; Takeda, Toshihiro; Ueda, Yasuyoshi; Petersen, Hans; Dancer, Robert; Ahmadian, Haleh; Lyngso, Lars Ole
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014821	A1	20040219	WO 2003-DK537	20030812

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,

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CA 2495118	A1	20040219	CA 2003-2495118	20030812	
AU 2003250321	A1	20040225	AU 2003-250321	20030812	
EP 1534654	A1	20050601	EP 2003-783962	20030812	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003013114	A	20050712	BR 2003-13114	20030812	
CN 1675144	A	20050928	CN 2003-819001	20030812	
JP 2005535322	T	20051124	JP 2004-526641	20030812	
NZ 537785	A	20061222	NZ 2003-537785	20030812	
CN 101045664	A	20071003	CN 2007-10101805	20030812	
ZA 2005000728	A	20060726	ZA 2005-728	20050125	
MX 2005001400	A	20050428	MX 2005-1400	20050203	
IN 2005CN00367	A	20070907	IN 2005-CN367	20050310	
NO 2005001292	A	20050314	NO 2005-1292	20050314	
US 20070129561	A1	20070607	US 2006-524937	20060216	
PRIORITY APPLN. INFO.:			DK 2002-1201	20020812	
			US 2002-403088P	20020812	
			CN 2003-819001	20030812	
			WO 2003-DK537	20030812	

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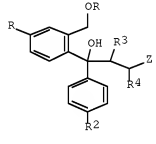


I

AB The (S)- or (R)-enantiomer of a diol I [R = CN or a group convertible to CN; R1 = H; R2 = halogen; R3, R4 = H; R3R4 = bond; Z = (un)substituted CH2NH2, a group convertible to CH2NMe2] and the opposite enantiomer of I [R1 = C(:W)YR5; W = O, S; Y = O, S, NH; R5 = (un)substituted alkyl, alkenyl, alkynyl] are prepared by enzymic acylation of I [R1 = H] or enzymic deacylation of I [R1 = C(:W)YR5]. Thus, I [R = CN, R, R3, R4 = H, R2 = F, Z = CH2NMe2] was treated with vinyl butyrate in the presence of Novozym 435 and pivalic acid to give (S)-I [R = CN, R, R3, R4 = H, R2 = F, Z = CH2NMe2] in 36.4% yield and 98.7% ee. (S)-I [R = CN, R, R3, R4 = H, R2 = F, Z = CH2NMe2] was converted to escitalopram oxalate of 98.5% ee.

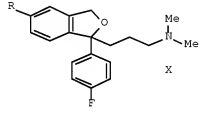
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 10 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 138:55857 MARPAT Full-text
TITLE: Process for the preparation of citalopram
INVENTOR(S): Hamied, Yusuf Khwaja; Kankan, Rajendra Narayanrao;

Rao, Dharmaraj Ramachandra
PATENT ASSIGNEE(S): Cipla Limited, India
SOURCE: Brit. UK Pat. Appl., 11 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2376945	A	20021231	GB 2001-15708	20010627

PRIORITY APPLN. INFO.: GB 2001-15708 20010627
OTHER SOURCE(S): CASREACT 138:55857
GI



I

AB An improved process for the preparation of citalopram via substitution of the halogen of halophthalane salts I (R = halogen; X = oxalate, fumarate, maleate, citrate, acetate, formate, hydrochloride, hydrobromide, sulfate) using cuprous cyanide in an organic solvent. Thus, bromophthalane oxalate I (R = Br, X = oxalate) was reacted CuCN in diglyme under a nitrogen atmospheric at 150-155° for 3 h to form citalopram which was converted to its HBr salt I (R = CN, X = HBr).
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 11 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 137:216863 MARPAT Full-text
TITLE: Preparation of phthalanes
INVENTOR(S): Hamied, Yusuf Khwaja; Kankan, Rajendra Narayanrao; Rao, Dhanmaraj Ramachandra
PATENT ASSIGNEE(S): Cipla Ltd., India; Wain, Christopher Paul
SOURCE: PCT Int. Appl., 11 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002070501	A1	20020912	WO 2002-GB1054	20020307

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,

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NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,
SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
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AU	2002236076	A1	20020919	AU 2002-236076	20020307
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EP	1366034	A1	20031203	EP 2002-702553	20020307
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,
PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

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HU	2003003467	A2	20040128	HU 2003-3467	20020307
TR	200301444	T2	20040921	TR 2003-1444	20020307
RU	2276148	C2	20060510	RU 2003-129659	20020307
AT	368035	T	20070815	AT 2002-702553	20020307
IN	2003MN00844	A	20050715	IN 2003-MN844	20030908
LT	5167	B	20041025	LT 2003-86	20030930
BG	108232	A	20050430	BG 2003-108232	20031006
LV	13132	B	20040620	LV 2003-107	20031007
ZA	2003008039	A	20041117	ZA 2003-8039	20031016
US	20040092755	A1	20040513	US 2003-471052	20031118
US	6903228	B2	20050607		
PRIORITY APPLN. INFO.:				GB 2001-5627	20010307
				WO 2002-GB1054	20020307

OTHER SOURCE(S): CASREACT 137:216863
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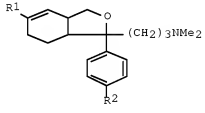

I

AB Citalopram and other phthalanes I [R1 = CN, R2 = halogen, trifluoromethyl, CN, acyl] are made by treating a salt of I [R1 = halogen] with cuprous cyanide. Thus, 100g I.oxalate [R1 = Br, R2 = F] was treated with 35 g CuCN in diglyme at 150-155° for 3 h to give 35 g I [R1 = CN, R2 = F] as the hydrobromide.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 12 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 135:257142 MARPAT Full-text
TITLE: Method for the preparation of citalopram
INVENTOR(S): Petersen, Hans
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068631	A1	20010920	WO 2001-DK168	20010313
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PT 1173431	T	20030930	PT 1999-913120	19990414
ES 2195554	T3	20031201	ES 1999-913120	19990414
CA 2402388	A1	20010920	CA 2001-2402388	20010313
AU 2001042298	A	20010924	AU 2001-42298	20010313
GR 2001100123	A	20021122	GR 2001-100123	20010313
GR 1004072	B2	20021202		
EP 1265883	A1	20021218	EP 2001-915098	20010313
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
TR 200202166	T2	20021223	TR 2002-2166	20010313
BR 2001009176	A	20030422	BR 2001-9176	20010313
HU 2003000274	A2	20030628	HU 2003-274	20010313
JP 2003527387	T	20030916	JP 2001-567723	20010313
NZ 521201	A	20040227	NZ 2001-521201	20010313
ZA 2002006899	A	20030828	ZA 2002-6899	20020828
BG 107047	A	20030430	BG 2002-107047	20020902
NO 2002004213	A	20021113	NO 2002-4213	20020904
US 20030092919	A1	20030515	US 2002-237145	20020905
US 6762308	B2	20040713		
MX 2002008869	A	20030210	MX 2002-8869	20020911
IN 2002CN01661	A	20050128	IN 2002-CN1661	20021010
US 20040215025	A1	20041028	US 2004-851595	20040521
US 6992198	B2	20060131		

PRIORITY APPLN. INFO.:		
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	DK 2000-415	20000314
	EP 1999-913120	19990414
	WO 2001-DK168	20010313
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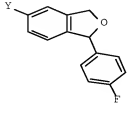

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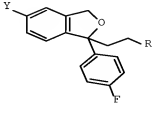

II

AB The present invention relates to a method for the preparation of citalopram, well-known antidepressant, by alkylation of a 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran derivative I [Y = a group which may be converted to CN group] with X(CH2)2R [X = a suitable leaving group; no R group definition] to form II, followed by, in either order, conversion of the group R to a dimethylaminomethyl group and conversion of the group Y to a CN group, followed by isolation of the citalopram (no preparative data given).
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 13 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 135:257141 MARPAT Full-text
TITLE: Method for the preparation of citalopram
INVENTOR(S): Petersen, Hans
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068630	A1	20010920	WO 2001-DK162	20010309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PT 1173431	T	20030930	PT 1999-913120	19990414
ES 2195554	T3	20031201	ES 1999-913120	19990414
CA 2402557	A1	20010920	CA 2001-2402557	20010309
BR 2001009268	A	20021203	BR 2001-9268	20010309
EP 1265882	A1	20021218	EP 2001-913738	20010309
EP 1265882	B1	20040114		
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TR 200202155	T2	20021223	TR 2002-2155	20010309
HU 20030001778	A2	20030528	HU 2003-178	20010309
JP 2003527386	T	20030916	JP 2001-567722	20010309
AT 257832	T	20040115	AT 2001-913738	20010309
PT 1265882	T	20040630	PT 2001-913738	20010309
ES 2214400	T3	20040916	ES 2001-913738	20010309
ZA 2002006897	A	20030828	ZA 2002-6897	20020828
BG 107051	A	20030530	BG 2002-107051	20020902
NO 2002004198	A	20020903	NO 2002-4198	20020903
MX 2002008653	A	20030224	MX 2002-8653	20020904
US 20030050484	A1	20030313	US 2002-238907	20020906
US 6806376	B2	20041019		
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PRIORITY APPLN. INFO.:			DK 2000-415	20000314
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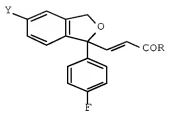

I

AB The invention relates to a method for the preparation of citalopram, well-known antidepressant, comprising, in either order, subjecting a compound I [Y = CN or a group which may be converted to CN group; R = H, OR1, NH2, NHMe, NMe2 (R1 = H, alkyl, alkenyl, alkynyl, (un)substituted aryl or aralkyl)] to reduction of the double bond in the side chain of formula -CH=CH-COR followed by conversion of the group -COR or its reduced form to a dimethylaminomethyl group; and then if Y is not cyano, conversion of the group Y to a cyano group; followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof (preparative data were not given). Preparation of compound I is also claimed.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 14 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 135:257140 MARPAT Full-text
TITLE: Stepwise alkylation of 5-substituted 1-(4-fluorophenyl)-1,3-dihydroisobenzofurans (citalopram intermediates)
INVENTOR(S): Petersen, Hans; Ahmadian, Haleh
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068629	A1	20010920	WO 2001-DK159	20010309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2402553	A1	20010920	CA 2001-2402553	20010309
EP 1265881	A1	20021218	EP 2001-913735	20010309
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

TR 200202195	T2	20021223	TR 2002-2195	20010309
BR 2001009364	A	20021224	BR 2001-9364	20010309
HU 2003000273	A2	20030628	HU 2003-273	20010309
JP 2003527385	T	20030916	JP 2001-567721	20010309
NZ 521204	A	20040326	NZ 2001-521204	20010309
BG 107046	A	20030530	BG 2002-107046	20020902
ZA 2002007024	A	20030902	ZA 2002-7024	20020902
MX 2002008684	A	20030224	MX 2002-8684	20020905
US 20030083509	A1	20030501	US 2002-242804	20020910
US 6864379	B2	20050308		
NO 2002004352	A	20021008	NO 2002-4352	20020912
IN 2002CN01662	A	20050128	IN 2002-CN1662	20021010
US 20050020670	A1	20050127	US 2004-917667	20040813
PRIORITY APPLN. INFO.:			DK 2000-403	20000313
			DK 2000-414	20000314
			WO 2001-DK159	20010309
			US 2002-242804	20020910

OTHER SOURCE(S): CASREACT 135:257140

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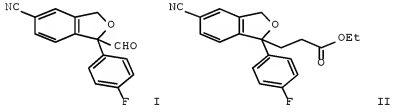

I II

AB Methods for manufacture of citalopram, well-known antidepressant, through stepwise alkylation of 5-R-substituted 1-(4-fluorophenyl)-1,3-dihydroisobenzofurans [R = CN, OH, NH2, etc.] are disclosed. Thus, reacting 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile with Me formate in the presence of LDA in THF followed by reacting the resulting 1-formyl intermediate I with tri-Et phosphonoacetate in the presence of LDA in THF, hydrogenation of the crude intermediate, and reacting the intermediate II with Me chloroaluminum dimethylamide in PhMe afforded citalopram.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 15 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 135:257139 MARPAT Full-text
TITLE: Method for the preparation of citalopram
INVENTOR(S): Petersen, Hans
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001068628	A1	20010920	WO 2001-DK149	20010307
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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CA 2402386	A1	20010920	CA 2001-2402386	20010307
AU 2001039203	A	20010924	AU 2001-39203	20010307
BR 2001009267	A	20021217	BR 2001-9267	20010307
EP 1265880	A1	20021218	EP 2001-913728	20010307
EP 1265880	B1	20041110		
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HU 2003000180	A2	20030528	HU 2003-180	20010307
JP 2003527384	T	20030916	JP 2001-567720	20010307
AT 282031	T	20041115	AT 2001-913728	20010307
NZ 521202	A	20041126	NZ 2001-521202	20010307
IT 2001MI0487	A1	20020909	IT 2001-MI487	20010308
FR 2806085	A1	20010914	FR 2001-3245	20010309
FR 2806085	B1	20050225		
BE 1011598	A6	20010703	BE 2001-159	20010313
ZA 2002006898	A	20040420	ZA 2002-6898	20020828
BG 107048	A	20030530	BG 2002-107048	20020902
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US 20030069304	A1	20030410	US 2002-238843	20020909
US 6717000	B2	20040406		
MX 2002008872	A	20030210	MX 2002-8872	20020911
IN 2002CN01663	A	20050128	IN 2002-CN1663	20021010
PRIORITY APPLN. INFO.:			DK 2000-404	20000313
			WO 2001-DK149	20010307

OTHER SOURCE(S): CASREACT 135:257139

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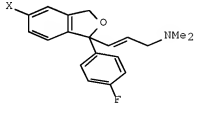

I

AB The present invention relates to a method for the preparation of citalopram, well-known antidepressant, comprising reduction of a compound I wherein X is a cyano group or a group which can be converted to a cyano group, and if X is not a cyano group followed by conversion of X to a cyano group (no preparative data given). Preparation of the compound I is also claimed.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE

RE FORMAT

L21 ANSWER 16 OF 16 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 87:135040 MARPAT Full-text
TITLE: Phthalan derivatives
INVENTOR(S): Boegesoe, Klaus Peter; Toft, Anders Stausboell
PATENT ASSIGNEE(S): Kefalas A/S, Den.
SOURCE: Ger. Offen., 30 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2657013	A1	19770728	DE 1976-2657013	19761216
DE 2657013	C2	19851114		
SE 7614201	A	19770715	SE 1976-14201	19761217
SE 429551	B	19830912		
SE 429551	C	19831222		
AT 7609472	A	19800415	AT 1976-9472	19761221
AT 359488	B	19801110		
AU 7721073	A	19780713	AU 1977-21073	19770105
AU 509445	B2	19800515		
US 4136193	A	19790123	US 1977-757619	19770107
FI 7700073	A	19770715	FI 1977-73	19770111
FI 63754	B	19830429		
FI 63754	C	19830810		
NL 7700244	A	19770718	NL 1977-244	19770112
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NO 7700109	A	19770715	NO 1977-109	19770113
NO 147243	B	19821122		
NO 147243	C	19830302		
JP 52105162	A	19770903	JP 1977-1997	19770113
JP 61035986	B	19860815		
CA 1094087	A1	19810120	CA 1977-269610	19770113
CH 626886	A5	19811215	CH 1977-423	19770113
BE 850401	A1	19770714	BE 1977-174098	19770114
DK 7700131	A	19770715	DK 1977-131	19770114
DK 143275	B	19810803		
DK 143275	C	19820118		
FR 2338271	A1	19770812	FR 1977-1079	19770114
FR 2338271	B1	19821105		
AT 7905719	A	19800515	AT 1979-5719	19790827
AT 360001	B	19801210		
AT 7905720	A	19800515	AT 1979-5720	19790827
AT 360002	B	19801210		
CH 632258	A5	19820930	CH 1981-3574	19810601
CH 632259	A5	19820930	CH 1981-3575	19810601

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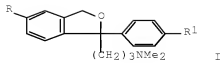

I

AB Phthalans I (R = Cl, Br, CF3, F, CN, COEt; R1 = Cl, F, Br, CN) were prepared Thus, 5-bromophthalide was treated with 4-ClC6H4MgBr, 4,2-Br(HOCH2)C6H3COC6H4Cl-4 treated with Me2N(CH2)3MgCl, and 4,2-Br(HOCH2)C6H3C(OH)(C6H4Cl-4)(CH2)3NMe2 cyclized with H3PO4 to give I (R = Br, R1 = Cl), which had ED50 in the tryptophan potentiation test of 4.6 mg/kg i.p.

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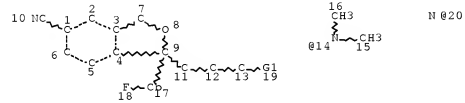

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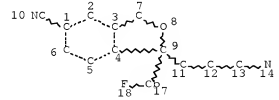

Str. – Claim 8 (a)

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GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  16

STEREO ATTRIBUTES: NONE
L25          15 SEA FILE=REGISTRY SUB=L23 SSS FUL L24

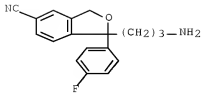
100.0% PROCESSED     125 ITERATIONS                          15 ANSWERS
SEARCH TIME: 00.00.01

     FILE 'CAPLUS' ENTERED AT 16:29:05 ON 05 MAR 2009
L26          82 S L25
L27           7 SEA ABB=ON  PLU=ON  L26(L)(OPTIAL? OR CHIRAL OR ENRIOMER?
                OR RESOLUT? OR METHYLAT?)
L28          11 SEA ABB=ON  PLU=ON  L26(L)(RACT OR RCT)/RL
L29          15 SEA ABB=ON  PLU=ON  L27 OR L28
L30          12 SEA ABB=ON  PLU=ON  L29 NOT (L8 OR L20)

E294 THROUGH E304 ASSIGNED

L30  ANSWER 1 OF 12  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        2008:1411319  CAPLUS  Full-text
DOCUMENT NUMBER:         150:55902
TITLE:                   Response to the Comments by Elati et al. in
                         Response to Our Article Examining One of Their
                         Previous Articles
AUTHOR(S):               Dancer, Robert James; Lopez De Diego, Heidi
CORPORATE SOURCE:        Department for Process Research and Department for
                         Preformulation, H. Lundbeck A/S, Valby, DK-2500,
                         Den.
SOURCE:                  Organic Process Research & Development (2009),
                         13(1), 38-43
                         CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER:               American Chemical Society
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   This reply highlights and discusses what we observe as internal
     inconsistencies in the data and anal. presented by Elati and coauthors in
     conjunction with their resolution protocols, as well as inconsistencies
     between their original manuscript, the associated patent, and the response to
     our disputing manuscript.  We address also their comments concerning their
     alkylation procedures.
IT   62498-69-5, Didesmethylcitalopram
     RL: PEP (Physical, engineering or chemical process); RCT
     (Reactant); PROC (Process); RACT (Reactant or reagent)
        (attempted resolution of citalopram and
        didesmethylcitalopram using di-p-toluoyltartaric acid)
RN   62498-69-5  CAPLUS
CN   5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-
     dihydro-  (CA INDEX NAME)
```

RACT-reactant/reagent; RCT-reactant

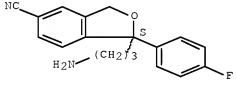


IT 928652-45-3P
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(attempted resolution of citalopram and didesmethylcitalopram using di-p-toluoyltartaric acid)
RN 928652-45-3 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2R,3R)-, compd. with (1S)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (1:1) (CA INDEX NAME)

CM 1

CRN 166037-78-1
CMF C18 H17 F N2 O

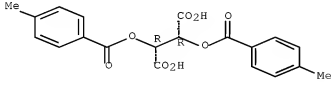
Absolute stereochemistry. Rotation (+).



CM 2

CRN 32634-66-5
CMF C20 H18 O8

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:1470458 CAPLUS Full-text
DOCUMENT NUMBER: 148:70178

TITLE: Modified serotonin reuptake inhibitors having peripheral system-restricted activity
INVENTOR(S): Rehavi, Moshe; Gurwitz, David
PATENT ASSIGNEE(S): Ramot at Tel Aviv University Ltd., Israel
SOURCE: PCT Int. Appl., 63pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007148341	A2	20071227	WO 2007-IL756	20070621
WO 2007148341	A3	20080214		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
EP 2029566	A2	20090304	EP 2007-736486	20070621
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR				

PRIORITY APPLN. INFO.:		
US 2006-815582P	P	20060622
WO 2007-IL756	W	20070621

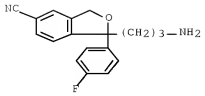
OTHER SOURCE(S): CASREACT 148:70178

AB The invention discloses serotonin reuptake inhibitor (SRI) compds. which are designed to exert serotonin uptake inhibitory activity in the peripheral system while being devoid of CNS activity. The invention also discloses a process of preparing these compds. The invention further discloses pharmaceutical compns. containing these compds. and uses thereof in the treatment of medical conditions associated with peripheral serotonin levels and/or activity, and/or platelet aggregation. The SRIs of the invention are modified so as to contain at least one pos.-charged group, e.g. a quaternary ammonium group. Preparation of N-Me citalopram is described.

IT 62498-69-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(modified serotonin reuptake inhibitors with peripheral system-restricted activity)

RN 62498-69-5 CAPLUS

CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



L30 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:691100 CAPLUS Full-text
DOCUMENT NUMBER: 147:234934
TITLE: Substrate modification approach to achieve efficient resolution: didesmethylcitalopram: a key intermediate for escitalopram. [Erratum to document cited in CA146:316708]
AUTHOR(S): Elati, Chandrashekar R.; Kolla, Naveenkumar; Vankawala, Pravinchandra J.; Gangula, Srinivas; Chalamala, Subrahmanyeswarara; Sundaram, Venkatraman; Bhattacharya, Apurba; Vurimidi, Himabindu; Mathad, Vijayavitthal T.
CORPORATE SOURCE: Department of Research and Development, Dr. Reddy's Laboratories Ltd., Hyderabad, 502325, India
SOURCE: Organic Process Research & Development (2007), 11(4), 780
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB On page 292, in last paragraph, the correct exptl. details should read: "S-(=)-1-(3-Dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3- dihydro-isobenzofuran-5-carbonitrile (s-(+)-1•(-)-DPTTA). A mixture of compound 1a (25 g. 0.077 mol) and acetonitrile (125 mL) was stirred at room temperature for 5 min, and then a solution of (-) DPTTA monohydrate (31.4 g, 0.077 mol) in acetonitrile (125 mL) was added and the mixture stirred for 10-15 min. To the resultant white precipitate was added methanol (20 mL) slowly at 70-75°, and the resulting clear solution was slowly cooled to room temperature After cooling the flask to 0-5° for 1.0-1.5 h, the resulting solid was filtered. The recrystn. with acetonitrile/methanol was repeated for two more times, and the resulting solid was filtered. The filtered cake was washed with acetonitrile (20 mL) and dried at 60-65° to afford 9.8 g of 1·(-)-DPTTA. Yield (%): 36 (calculated relative to theor. which is half of the starting racemate). The DPTTA salt was hydrolyzed to afford escitalopram free base (1). [α]D for free base = 10.8 (c 1, methanol); chiral purity: 98.4%, H NMR for free base (200 MHz, DMSO-d6): 1.18-1.28 (m, 2H), 2.01 (s, 6H), 2.11-2.18 (m,4H), 5.11-5.20 (q,J=13.2 and 11.2 Hz, 2H), 7.12-7.16 (t, J + 8.8Hz, 2H), 7.56-7.59 (dd, j+5.2 and 3.6 Hz, 2H), 7.73-7.78 (m, 3H); MS (APCI) m/z 325 (M+ = 1).".

IT 928652-45-3P 928652-49-7P 928652-54-4P
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(resolution of didesmethylcitalopram and further methylation to enantiopure escitalopram (Erratum))

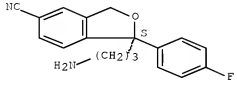
RN 928652-45-3 CAPLUS

CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2R,3R)-, compd. with (1S)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (1:1) (CA INDEX NAME)

CM 1

CRN 166037-78-1
CMF C18 H17 F N2 O

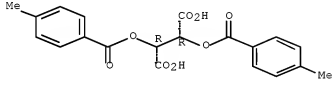
Absolute stereochemistry. Rotation (+).



CM 2

CRN 32634-66-5
CMF C20 H18 O8

Absolute stereochemistry. Rotation (-).

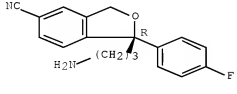


RN 928652-49-7 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2S,3S)-, compd. with (1R)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (1:1) (CA INDEX NAME)

CM 1

CRN 166037-77-0
CMF C18 H17 F N2 O

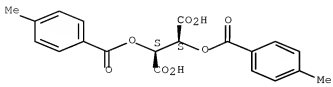
Absolute stereochemistry. Rotation (-).



CM 2

CRN 32634-68-7
CMF C20 H18 O8

Absolute stereochemistry. Rotation (+).

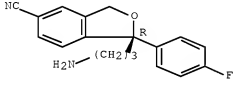


RN 928652-54-4 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2R,3R)-, compd. with (1R)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (1:1) (CA INDEX NAME)

CM 1

CRN 166037-77-0
CMF C18 H17 F N2 O

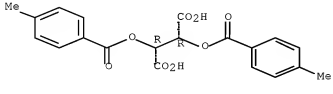
Absolute stereochemistry. Rotation (-).



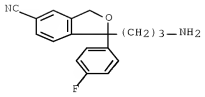
CM 2

CRN 32634-66-5
CMF C20 H18 O8

Absolute stereochemistry. Rotation (-).

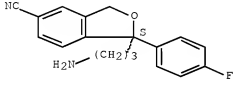


IT 62498-69-5 166037-78-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(resolution of didesmethylcitalopram and further methylation to enantiopure escitalopram (Erratum))
RN 62498-69-5 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)

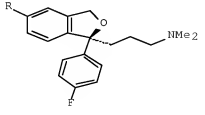


RN 166037-78-1 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1S)- (CA INDEX NAME)

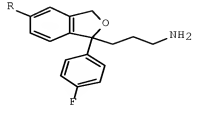
Absolute stereochemistry. Rotation (+).



L30 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:52599 CAPLUS Full-text
DOCUMENT NUMBER: 146:316708
TITLE: Substrate Modification Approach to Achieve Efficient Resolution: Didesmethylcitalopram: A Key Intermediate for Escitalopram
AUTHOR(S): Elati, Chandrashekar R.; Kolla, Naveenkumar; Vankawala, Pravinchandra J.; Gangula, Srinivas; Chalamala, Subrahmanyeswarara; Sundaram, Venkatraman; Bhattacharya, Apurba; Vurimidi, Himabindu; Mathad, Vijayavitthal T.
CORPORATE SOURCE: Department of Research and Development, Dr. Reddy's Laboratories Ltd., Hyderabad, 502325, India
SOURCE: Organic Process Research & Development (2007), 11(2), 289-292
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:316708
GI



I



II

AB An approach to achieve the enantiopure escitalopram I (R = CN or Br) via didesmethyl escitalopram II, which is easily resolvable compared to citalopram I (R = CN) through diastereomeric salt crystallization was reported. The resolved intermediate (didesmethylcitalopram) was subsequently used for the preparation of the desired drug. This simple modification of the substrate makes a remarkable difference in the chemical resolution process. The first resolution of didesmethylcitalopram (±)-II to furnish (+)-II, a novel key intermediate to assemble escitalopram I (R = CN) was achieved via diastereomeric salt resolution using (-)-di-p-toluoyltartaric acid (DPTTA). The resolution conditions were optimized; a key feature of this process is the addition of specific quantity of water at a specific temperature to the reaction mixture

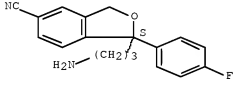
IT 928652-45-3P 928652-49-7P 928652-54-4P
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(resolution of didesmethylcitalopram and further methylation to enantiopure escitalopram)

RN 928652-45-3 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2R,3R)-, compd. with (1S)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (1:1) (CA INDEX NAME)

CM 1

CRN 166037-78-1
CMF C18 H17 F N2 O

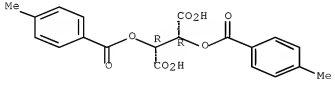
Absolute stereochemistry. Rotation (+).



CM 2

CRN 32634-66-5
CMF C20 H18 O8

Absolute stereochemistry. Rotation (-).



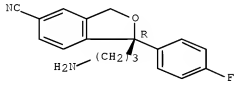
RN 928652-49-7 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2S,3S)-, compd. with (1R)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-

isobenzofurancarbonitrile (1:1) (CA INDEX NAME)

CM 1

CRN 166037-77-0
CMF C18 H17 F N2 O

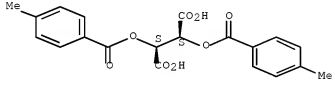
Absolute stereochemistry. Rotation (-).



CM 2

CRN 32634-68-7
CMF C20 H18 O8

Absolute stereochemistry. Rotation (+).

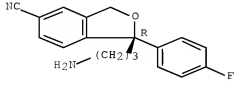


RN 928652-54-4 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2R,3R)-, compd. with (1R)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (1:1) (CA INDEX NAME)

CM 1

CRN 166037-77-0
CMF C18 H17 F N2 O

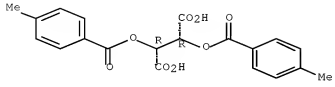
Absolute stereochemistry. Rotation (-).



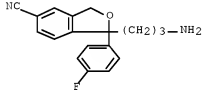
CM 2

CRN 32634-66-5
CMF C20 H18 O8

Absolute stereochemistry. Rotation (-).

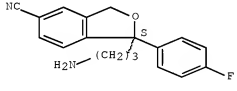


IT 62498-69-5 166037-78-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(resolution of didesmethylcitalopram and further methylation to enantiopure escitalopram)
RN 62498-69-5 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



RN 166037-78-1 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:962035 CAPLUS Full-text
DOCUMENT NUMBER: 143:242033
TITLE: Treatment or prophylaxis of migraine or headache disorders using citalopram, escitalopram or citalopram metabolites
INVENTOR(S): Barberich, Timothy
PATENT ASSIGNEE(S): Sepracor Inc., USA

SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005079787	A1	20050901	WO 2005-US5111	20050217
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005215790	A1	20050901	AU 2005-215790	20050217
CA 2556424	A1	20050901	CA 2005-2556424	20050217
US 20050192344	A1	20050901	US 2005-60067	20050217
EP 1720541	A1	20061115	EP 2005-723234	20050217
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, HR, LV, MK, YU				
JP 2007523176	T	20070816	JP 2006-554214	20050217
IN 2005CN02330	A	20070824	IN 2005-CN2330	20050920

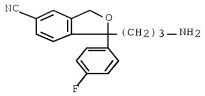
PRIORITY APPLN. INFO.: US 2004-545710P P 20040217
WO 2005-US5111 W 20050217

AB Methods for treating or preventing migraine or migraine headaches or other headache disorders include administering a therapeutically effective amount of citalopram, escitalopram, or a racemic or optically pure citalopram metabolite, or pharmaceutically acceptable salts, solvates, polymorphs, or hydrates thereof. Preparation of e.g. metabolites is included.

IT 62498-69-5P, Didesmethylcitalopram 166037-77-0P
166037-78-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(citalopram, escitalopram or citalopram metabolites for treatment or prophylaxis of migraine or headache disorders)

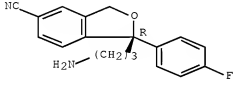
RN 62498-69-5 CAPLUS

CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



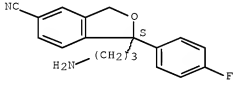
RN 166037-77-0 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 166037-78-1 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



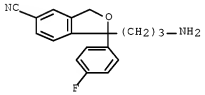
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:684021 CAPLUS Full-text
DOCUMENT NUMBER: 139:369875
TITLE: Enantiomeric separation of citalopram and its metabolites by capillary electrophoresis
AUTHOR(S): Mandrioli, Roberto; Fanali, Salvatore; Pucci, Vincenzo; Raggi, Maria A.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Bologna, Bologna, Italy
SOURCE: Electrophoresis (2003), 24(15), 2608-2616
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A simple and fast capillary electrophoretic method was developed for the enantioselective separation of citalopram and its main metabolites, namely N-

desmethylcitalopram and N,N-didesmethylcitalopram, using β-cyclodextrin (β-CD) sulfate as the chiral selector. For method optimization several parameters were investigated, such as CD and buffer concentration, buffer pH, and capillary temperature Baseline enantiosepn. of the racemic compds. was achieved in less than 6 min using a fused-silica capillary, filled with a background electrolyte consisting of a 35 mM phosphate buffer at pH 2.5 supplemented with 1% w/v β-CD sulfate and 0.05% w/v β-CD at 25°C and applying a voltage of -20 kV. A fast separation method for citalopram was also optimized and applied to the anal. of pharmaceutical formulations. Racemic citalopram was resolved in its enantiomers in less than 1.5 min using short-end injection (8.5 cm, effective length) running the expts. in a background electrolyte composed of a 25 mM citrate buffer at pH 5.5 and 0.04% w/v β-CD sulfate at a temperature of 10°C.

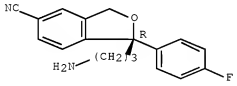
IT 62498-69-5 166037-77-0 166037-78-1
RL: ANT (Analyte); ANST (Analytical study)
(resolution of citalopram and metabolites by capillary electrophoresis)

RN 62498-69-5 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



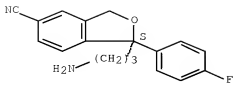
RN 166037-77-0 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 166037-78-1 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



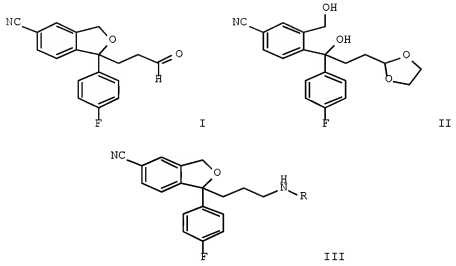
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:376842 CAPLUS Full-text
DOCUMENT NUMBER: 138:385297
TITLE: Methods for treating depression and other CNS disorders using enantiomerically enriched desmethyl- and didesmethyl- metabolites of citalopram
INVENTOR(S): Bush, Larry R.; Currie, Mark G.; Senanayake, Chris H.; Fang, Kevin Q.
PATENT ASSIGNEE(S): Sepracor, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003040121	A1	20030515	WO 2002-US35408	20021105
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2465186	A1	20030515	CA 2002-2465186	20021105
AU 2002356903	A1	20030519	AU 2002-356903	20021105
AU 2002356903	A2	20030519		
EP 1446396	A1	20040818	EP 2002-802848	20021105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013949	A	20040831	BR 2002-13949	20021105
HU 2004001934	A2	20050128	HU 2004-1934	20021105
HU 2004001934	A3	20070529		
JP 2005510518	T	20050421	JP 2003-542167	20021105
CN 1705654	A	20051207	CN 2002-822084	20021105
NZ 532478	A	20070223	NZ 2002-532478	20021105
IN 2004KN00505	A	20060616	IN 2004-KN505	20040419
ZA 2004003409	A	20051026	ZA 2004-3409	20040505
MX 2004004368	A	20040811	MX 2004-4368	20040507
US 20040266864	A1	20041230	US 2004-842055	20040507

NO 2004002013 A 20040514 NO 2004-2013 20040514
PRIORITY APPLN. INFO.: US 2001-337608P P 20011108
WO 2002-US35408 W 20021105

GI



AB This invention relates to the preparation of I and II and derivs. of I and II in their racemic, enantiomerically enriched, or optically pure forms. This invention further relates to novel compns. of matter containing enantiomerically enriched (-)-desmethylcitalopram (-)-III (R = Me), (+)-didesmethylcitalopram (+)-III (R = Me), or (-)-didesmethylcitalopram (-)-III (R = H) or mixts. thereof in optimal ratios. Contrary to prior teachings, the enantiomerically enriched citalopram metabolites disclosed herein possess potent serotonin reuptake inhibitory activity, with minimal inhibitory effects on the reuptake of other known monoamines, e.g., norepinephrine (NE) or dopamine (DA). For example, stepwise reaction of 1-oxo-1,3-dihydroisobenzofuran-5-carbonitrile with 4-fluorophenylmagnesium bromide and the chiral Grignard reagent, which was prepared from 2-(2-bromoethyl)-[1,3]dioxolane and Mg powder, in THF gave II. Cyclization using mesyl chloride in CH2Cl2, followed by reduction provided the I. Reaction of the aldehyde with (-)-tert-butylsulfinamide in the presence of Ti(OEt)4 in EtOH afforded the sulfinamide, which was reduced to the amine III (R = H) with 10% HCl in MeOH. Protection of the amine with BOC anhydride in the presence of TEA in CH2Cl2 provided the enantiomerically enriched isomers, which were separated on a chiral column and subsequently deprotected with TFA to give (+)-III (R = H) and (-)-III (R = H). In biol. assays, (-)-III (R = H) and (+)-III (R = H) strongly inhibited serotonergic 5-HT receptor activity with Ki values of 5.8 nM and 90 nM, resp., with little effect on NE and DA transporter activity. By comparison, racemic citalopram inhibited serotonin reuptake with a Ki of 3.9 nM. The present invention also discloses methods for treating disorders, dysfunctions and diseases for which inhibition of serotonin reuptake is therapeutically beneficial. In particular, the present invention discloses a method for treating various forms of depression and other CNS disorders with pharmaceutical compns. described herein.

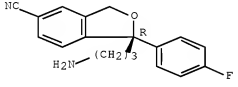
IT 526204-40-0 526204-41-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of enantiomerically enriched desmethyl- and didesmethyl-metabolites of citalopram for treating depression and other CNS disorders)

RN 526204-40-0 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1R)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 166037-77-0
CMF C18 H17 F N2 O

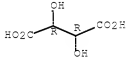
Absolute stereochemistry. Rotation (-).



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.

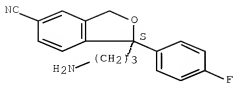


RN 526204-41-1 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1S)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 166037-78-1
CMF C18 H17 F N2 O

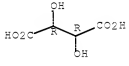
Absolute stereochemistry. Rotation (+).



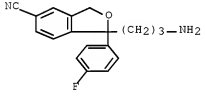
CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



IT 62498-69-5P, Rac-Didesmethylcitalopram
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(serotonin reuptake inhibitor; preparation of enantiomerically enriched desmethyl- and didesmethyl- metabolites of citalopram for treating depression and other CNS disorders)
RN 62498-69-5 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:90035 CAPLUS Full-text
DOCUMENT NUMBER: 136:135020
TITLE: Synthesis of amino acid derivatives for pharmaceutical use as glycine transport protein antagonists
INVENTOR(S): Moltzen, Ejner Knud; Smith, Garrick Paul; Krog-Jensen, Christian; Bogeso, Klaus Peter
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.

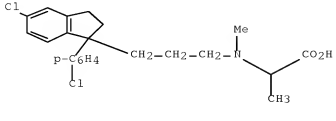
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008216	A1	20020131	WO 2001-DK510	20010719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2416447	A1	20020131	CA 2001-2416447	20010719
EP 1301502	A1	20030416	EP 2001-960184	20010719
EP 1301502	B1	20050518		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001013011	A	20030701	BR 2001-13011	20010719
HU 2003002778	A2	20031229	HU 2003-2778	20010719
HU 2003002778	A3	20050228		
JP 2004504393	T	20040212	JP 2002-514122	20010719
NZ 523720	A	20040730	NZ 2001-523720	20010719
AT 295844	T	20050615	AT 2001-960184	20010719
CN 1662519	A	20050831	CN 2001-815857	20010719
ES 2238466	T3	20050901	ES 2001-960184	20010719
PT 1301502	T	20050930	PT 2001-960184	20010719
AU 2001281740	B2	20060216	AU 2001-281740	20010719
IL 153988	A	20061005	IL 2001-153988	20010719
NO 2003000243	A	20030306	NO 2003-243	20030117
US 20030181445	A1	20030925	US 2003-348490	20030117
US 6921774	B2	20050726		
ZA 2003000514	A	20040820	ZA 2003-514	20030120
MX 2003000642	A	20030606	MX 2003-642	20030121
BG 107530	A	20030930	BG 2003-107530	20030205
IN 2003CN00223	A	20050408	IN 2003-CN223	20030205

PRIORITY APPLN. INFO.:

DK 2000-1124	A	20000721
WO 2001-DK510	W	20010719

OTHER SOURCE(S): MARPAT 136:135020
GI



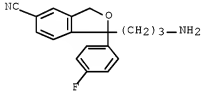
I

AB Title compds. (e.g., (I)), were prepared and tested as inhibitors of the glycine transport protein, for use in treatment of diseases responsive to ligands of the glycine transporter. Condensation of a 3-activated-prop-1-yl compound with an N-methylated amino acid ester, followed by ester hydrolysis, gave I-type compds. or their salts. Alternately, a suitable 3-aminoprop-1-yl compound was reacted with Et bromoacetate. In in vivo inhibition tests using human GlyT-1b, I had IC50 of 470 (sic).

IT 62498-69-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of amino acid derivs. for pharmaceutical use as glycine transport protein antagonists)

RN 62498-69-5 CAPLUS

CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2001:565627 CAPLUS Full-text

DOCUMENT NUMBER: 135:349029

TITLE: Optimization and characterization of the chiral separation of citalopram and its demethylated metabolites by response-surface methodology

AUTHOR(S): Carlsson, B.; Norlander, B.

CORPORATE SOURCE: Division of Clinical Pharmacology, Department of Medicine and Care, Faculty of Health Science, Linkoping University, Linkoping, 58185, Swed.

SOURCE: Chromatographia (2001), 53(5/6), 266-272
CODEN: CHRGB7; ISSN: 0009-5893

PUBLISHER: Friedrich Vieweg & Sohn Verlagsgesellschaft mbH

DOCUMENT TYPE: Journal

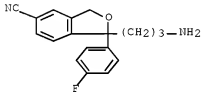
LANGUAGE: English

AB Response-surface modeling and sequential optimization have been used for optimization and characterization of the separation of the enantiomers of citalopram, desmethylcitalopram, and didesmethylcitalopram on an acetylated β-cyclodextrin column. In the model chosen the separation conditions mobile phase methanol content, buffer concentration, column temperature, and pH were varied to investigate their influence on the chromatog. It was found that what is good for selectivity within an enantiomer pair is bad for selectivity between enantiomer pairs. Because within-pair and between-pair selectivity does not reach its optimum at the same conditions, a middle course approach has to be followed. Use of an exptl. design for this investigation enabled understanding of the mechanisms of within- and between-pair separation for citalopram, desmethylcitalopram, and didesmethylcitalopram. Sequential

optimization can be a quicker means of optimizing a chromatog. separation; response-surface modeling, in addition to enabling optimization of the chromatog. process, also serves as a tool for learning more about the separation mechanism.

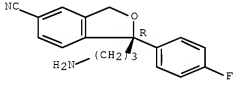
IT 62498-69-5 166037-77-0 166037-78-1
371770-06-8 371770-07-9 371770-08-0
RL: ANT (Analyte); ANST (Analytical study)
(resolution of citalopram and demethylated metabolites by HPLC using chemometric programs to optimize chromatog. conditions by response-surface methodol.)

RN 62498-69-5 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



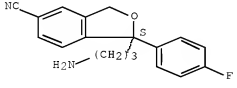
RN 166037-77-0 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 166037-78-1 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 371770-06-8 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (2R,3R)-2,3-dihydroxybutanedioate (9CI) (CA INDEX NAME)

CM 1

CRN 62498-69-5
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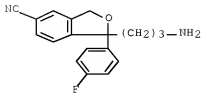
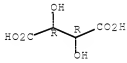


CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.

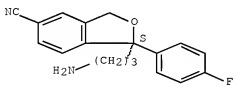


RN 371770-07-9 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1S)-, (2R,3R)-2,3-dihydroxybutanedioate (9CI) (CA INDEX NAME)

CM 1

CRN 166037-78-1
CMF C18 H17 F N2 O

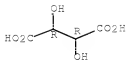
Absolute stereochemistry. Rotation (+).



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.

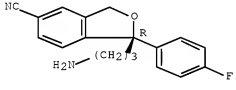


RN 371770-08-0 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1R)-, (2R,3R)-2,3-dihydroxybutanedioate (9CI) (CA INDEX NAME)

CM 1

CRN 166037-77-0
CMF C18 H17 F N2 O

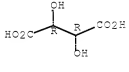
Absolute stereochemistry. Rotation (-).



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:452790 CAPLUS Full-text
DOCUMENT NUMBER: 135:61223
TITLE: Preparation of citalopram from 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.
INVENTOR(S): Rock, Michael Harold; Ahmadian, Haleh
PATENT ASSIGNEE(S): H. Lundbeck A/S, Den.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001043525	A2	20010621	WO 2001-DK123	20010222
WO 2001043525	A3	20020131		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
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ES 2195554	T3	20031201	ES 1999-913120	19990414
NL 1017414	C1	20010315	NL 2001-1017414	20010221
NL 1017415	C1	20010518	NL 2001-1017415	20010221
FR 2805812	A1	20010907	FR 2001-2339	20010221
FR 2805813	A1	20010907	FR 2001-2341	20010221
BE 1012921	A6	20010508	BE 2001-118	20010222
CA 2401236	A1	20010621	CA 2001-2401236	20010222
AU 2001035358	A	20010625	AU 2001-35358	20010222
CA 2400682	A1	20010830	CA 2001-2400682	20010222
WO 2001062754	A1	20010830	WO 2001-DK122	20010222
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GR 2001100097	A	20011031	GR 2001-100097	20010222
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HU 2003000212	A2	20030628	HU 2003-212	20010222
JP 2003523955	T	20030812	JP 2001-544478	20010222
JP 2003524009	T	20030812	JP 2001-562536	20010222
CN 1161350	C	20040811	CN 2001-805519	20010222
CN 1608057	A	20050420	CN 2001-805556	20010222
BE 1011177	A6	20010703	BE 2001-126	20010223
US 20010027256	A1	20011004	US 2001-794762	20010226
US 6420574	B2	20020716		
US 20020004604	A1	20020110	US 2001-794755	20010226
GR 2001100123	A	20021122	GR 2001-100123	20010313
GR 1004072	B2	20021202		

ZA 2002006255	A	20031020	ZA 2002-6255		20020806
NO 2002003928	A	20020819	NO 2002-3928		20020819
BG 107015	A	20030530	BG 2002-107015		20020820
ZA 2002006699	A	20031121	ZA 2002-6699		20020821
NO 2002004007	A	20021007	NO 2002-4007		20020822
US 20030083508	A1	20030501	US 2002-228388		20020823
MX 2002008230	A	20030523	MX 2002-8230		20020823
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BG 107061	A	20030530	BG 2002-107061		20020904
IN 2002CN01483	A	20050128	IN 2002-CN1483		20020918
IN 2002CN01512	A	20050128	IN 2002-CN1512		20020923
US 20030114692	A1	20030619	US 2002-286407		20021101
HK 1054378	A1	20050429	HK 2003-106541		20030911
PRIORITY APPLN. INFO.:			DK 2000-296	A	20000224
			DK 2000-401	A	20000313
			EP 1999-913120	A	19990414
			WO 2001-DK122	W	20010222
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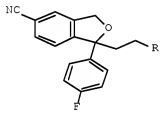
			US 2001-794755	A1	20010226

OTHER SOURCE(S): CASREACT 135:61223; MARPAT 135:61223

GI



II

AB Citalopram was prepared by reaction of 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (I) with XCH2CH2R (X = leaving group; R = CH2OPg, CH2NPg1Pg2, CONMe2, etc.; Pg, Pg1, Pg2 = protecting group) to give intermediate (II) followed by conversion of the R group to form a dimethylaminomethyl group and isolation. Thus, I in THF was added to LDA in THF at -78° followed by stirring for 30 min; PhCH2O(CH2)3Br in THF was added followed by warming to room temperature and stirring for 2 h to give 60% 1-[(3-benzyloxy)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. The latter was refluxed 2 days with 1,4-cyclohexadiene and Pd/C in EtOH to give 80% 1-(4-fluorophenyl)-1-(3-hydroxypropyl)- 1,3-dihydroisobenzofuran-5-carbonitrile. This was converted to the tosylate (42%) which was heated with Et3N and Me2NH.HCl in DMF at 70° overnight to give 70% citalopram as the oxalate.

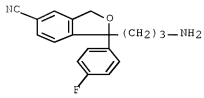
IT 62498-69-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of citalopram from fluorophenyldihydroisobenzofurancarbonitrile)

RN 62498-69-5 CAPLUS

CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1998:812048 CAPLUS Full-text

DOCUMENT NUMBER: 130:133592

TITLE: Analysis of the enantiomers of citalopram and its demethylated metabolites using chiral liquid chromatography

AUTHOR(S): Kosel, M.; Eap, C. B.; Amey, M.; Baumann, P.

CORPORATE SOURCE: Unite de Biochimie et Psychopharmacologie Clinique, Department Universitaire de Psychiatrie Adulte, Prilly-Lausanne, CH-1800, Switz.

SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1998), 719(1 + 2), 234-238 CODEN: JCBBEP; ISSN: 0378-4347

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

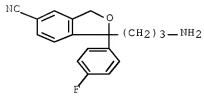
AB A procedure using a Chirobiotic V column is presented which allows separation of the enantiomers of citalopram and its 2 N-demethylated metabolites, and of the internal standard, alprenolol, in human plasma. Citalopram, demethylcitalopram and didemethylcitalopram, as well as the internal standard, were recovered from plasma by liquid-liquid extraction The limits of quantification were 5 ng/mL for each enantiomer of citalopram and demethylcitalopram, and 7.5 ng/mL for each enantiomer of didemethylcitalopram. Inter- and intra-day coeffs. of variation varied from 2.4 to 8.6% for S- and R-citalopram, from 2.9 to 7.4% for S- and R-demethylcitalopram, and from 5.6 to 12.4% for S- and R- didemethylcitalopram. No interference was observed from endogenous compds. following the extraction of plasma samples from 10 different patients treated with citalopram. This method allows accurate quantification for each enantiomer and is, therefore, well suited for pharmacokinetic and drug interaction investigations. The presented method replaces a previously described highly sensitive and selective HPLC procedure using an acetylated β-cyclobond column which, because of manufacture problems, is no longer usable for the separation of the enantiomers of citalopram and its demethylated metabolites.

IT 62498-69-5, Didemethylcitalopram 166037-77-0 166037-78-1

RL: ANT (Analyte); ANST (Analytical study)

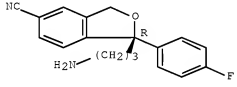
(separation of enantiomers of citalopram and demethylated metabolites by chiral HPLC)

RN 62498-69-5 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



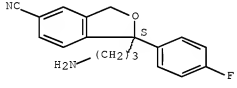
RN 166037-77-0 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 166037-78-1 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

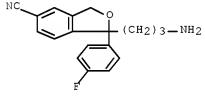
L30 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1995:886975 CAPLUS Full-text
DOCUMENT NUMBER: 123:329128
ORIGINAL REFERENCE NO.: 123:58713a,58716a
TITLE: Determination of the enantiomers of citalopram, its demethylated and propionic acid metabolites in human plasma by chiral HPLC
AUTHOR(S): Rochat, B.; Amey, M.; Van Gelderen, H.; Testa, B.; Baumann, P.
CORPORATE SOURCE: Univ. Psychiatrie Adulte, Prilly-Lausanne, Switz.
SOURCE: Chirality (1995), 7(6), 389-95

CODEN: CHRLEP; ISSN: 0899-0042
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A stereoselective HPLC assay has been developed to analyze the enantiomers of citalopram and of its three main metabolites in plasma after their separation on a Chiracel OD column. Using a fluorescence detector, the limit of quantification in plasma samples was 15, 4, 5, and 2 ng/mL for the enantiomers of citalopram (CIT), desmethylcitalopram (DCIT), didesmethylcitalopram (DDCIT), and for the citalopram propionic acid derivative (CIT-PROP), resp. Except for CIT, all metabolites were derivatized with achiral reagents. Identification of the enantiomers was realized with an optical rotation detector which showed that the enantiomers invert their rotation depending on the polarity and nature of the solvent. Under varying conditions, a racemization study has shown that the pure enantiomers of CIT and its demethylated metabolites are configurationally stable. Preliminary results obtained with five patients treated with CIT show a mean S/R ratio of 0.7 for both CIT and its active metabolite DCIT and of 3.6 for CIT-PROP in plasma. This suggests that the pharmacol. relevant (+)-(S)-isomers of CIT and DCIT could be preferentially and stereoselectively metabolized to CIT-PROP.

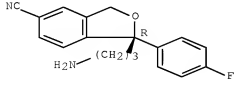
IT 62498-69-5, Didesmethylcitalopram 166037-77-0
166037-78-1
RL: ANT (Analyte); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative)
(determination of the enantiomers of citalopram, its demethylated and propionic acid metabolites in human plasma by chiral HPLC)

RN 62498-69-5 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro- (CA INDEX NAME)



RN 166037-77-0 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-, (1R)- (CA INDEX NAME)

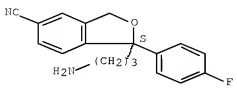
Absolute stereochemistry. Rotation (-).



RN 166037-78-1 CAPLUS
CN 5-Isobenzofurancarbonitrile, 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-

dihydro-, (1S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



(FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 16:36:47 ON 05 MAR 2009)

L31 63 SEA ABB=ON PLU=ON L25
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L33 0 SEA ABB=ON PLU=ON L31(L)(REACT? OR REAGENT OR RXN)
L34 12 SEA ABB=ON PLU=ON L31 AND (REACT? OR REAGENT OR RXN)
L35 10 SEA ABB=ON PLU=ON L31 AND (OPTIAL? OR CHIRAL OR ENRIOMER? OR RESOLUT? OR METHYLAT?)
L36 19 SEA ABB=ON PLU=ON L34 OR L35
L37 18 DUP REM L36 (1 DUPLICATE REMOVED)

L37 ANSWER 1 OF 18 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2007583352 EMBASE Full-text
TITLE: Therapeutic drug monitoring of escitalopram in an outpatient setting.
AUTHOR: Reis, Margareta, Dr. (correspondence); Cherma, Maria D.; Carlsson, Bjorn; Bengtsson, Finn
CORPORATE SOURCE: Department of Clinical Pharmacology, Faculty of Health Sciences, Linkoping University Hospital, Linkoping, Sweden. margareta.reis@med.lu.se
AUTHOR: Bengtsson, Finn
CORPORATE SOURCE: Department of Task Force.
AUTHOR: Reis, Margareta, Dr. (correspondence)
CORPORATE SOURCE: Institute of Laboratory Medicine, Department of Clinical and Experimental Pharmacology, Lund University Hospital, 221 85 Lund, Sweden. margareta.reis@med.lu.se
SOURCE: Therapeutic Drug Monitoring, (Dec 2007) Vol. 29, No. 6, pp. 758-766.
Refs: 36
ISSN: 0163-4356 CODEN: TDMODV
PUBLISHER IDENT.: 00007691200712000000007
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Dec 2007
Last Updated on STN: 27 Dec 2007

AB The main objectives of this study were to outline the inter- and intraindividual and overall pharmacokinetic variability of S-citalopram, S-desmethylcitalopram, and S-didesmethylcitalopram in serum by means of therapeutic drug monitoring; and to investigate potential correlations between the serum concentration and simultaneously collected clinical data. The study was conducted on outpatients in Sweden in 2002 to 2005. Included in the pharmacokinetic evaluation were 155 patients (68% women and 32% men) aged 17

to 95 years (average, 51 years). One serum sample per patient, taken as a trough value in steady state, was assessed. For the inter- and intraindividual variation calculation, 16 patients were included with two eligible samples each. The median daily dose was 20 mg/day (range, 5-40 mg). Extensive overall serum concentration variability was seen for all dose levels. The interindividual coefficient of variation for dose-normalized concentrations was 71% for S-citalopram, 36% for S-desmethylcitalopram, and 50% for S- didesmethylcitalopram. The intraindividual variations over time for the same parameters were approximately 30%, except for the ratio S-desmethylcitalopram/S- citalopram, which was 23%. The median S-desmethylcitalopram level was approximately 60% of the parent substance and the S-didesmethylcitalopram level approximately 9%. Higher age was correlated with higher serum concentrations, but no gender-related concentration differences were found. A majority (76%) of the patients took one or more drugs in addition to escitalopram, but concomitant medication did not seem to interact with escitalopram. However, women taking oral contraceptives showed a lower metabolic ratio compared with age-matched women. As a result of the wide range of the ratio in this population, these findings are not considered of clinical relevance. .COPYRGT. 2007 Lippincott Williams & Wilkins, Inc.

L37 ANSWER 2 OF 18 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER:	2007411603 EMBASE Full-text
TITLE:	Quantification of eight new antidepressants and five of their active metabolites in whole blood by high-performance liquid chromatography-tandem mass spectrometry.
AUTHOR:	Castaing, Nadege; Titier, Karine (correspondence); Receveur-Daurel, Mathilde; Le-Deodic, Maite; Le-Bars, Delphine; Moore, Nicholas; Molimard, Mathieu
CORPORATE SOURCE:	Department of Clinical Pharmacology and Toxicology, Pellegrin Hospital, University Victor Segalen, 33076 Bordeaux, France. karine.titier@pharmaco.u-bordeaux2.fr
AUTHOR:	Titier, Karine (correspondence)
CORPORATE SOURCE:	Laboratoire de Pharmacologie Clinique et de Toxicologie, Hopital Pellegrin, Place Amelie Raba-Leon, 33076 Bordeaux Cedex, France. karine.titier@pharmaco.u-bordeaux2.fr
SOURCE:	Journal of Analytical Toxicology, (Jul 2007) Vol. 31, No. 6, pp. 334-341. Refs: 21 ISSN: 0146-4760 E-ISSN: 0146-4760 CODEN: JATOD3
COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article
FILE SEGMENT:	027 Biophysics, Bioengineering and Medical Instrumentation 037 Drug Literature Index 049 Forensic Science Abstracts 052 Toxicology
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 5 Sep 2007 Last Updated on STN: 5 Sep 2007

AB A liquid chromatography-tandem mass spectrometry method is described for the blood determination of selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram), serotonin noradrenaline reuptake inhibitors (milnacipram and venlafaxine), a noradrenergic and specific serotoninergic antidepressant (mirtazapine) and five of their active metabolites (norfluoxetine, desmethylcitalopram, didesmethylcitalopram,

desmethylvenlafaxine, and desmethylmirtazapine). After a liquid-liquid extraction from blood, the compounds and the internal standard (methylrisperidone) were eluted on a XTerra® RP18 column with a gradient of acetonitrile/ammonium formate buffer 4 mmol/L pH 3.2. They were then detected by electrospray ionization mass spectrometry with multiple reaction monitoring mode. The calibration curves were linear over the range 5-500 ng/mL (20-2000 ng/mL for venlafaxine and desmethylvenlafaxine). The limit of quantification was set at 5 ng/mL for each compound (except for venlafaxine and desmethylvenlafaxine: 20 ng/mL). The bias were lower than 12%. Intraday and interday precisions, expressed as variation coefficient, were lower than 11%. The extraction recoveries were between 70 and 90% except for desmethylmirtazapine, desmethylvenlafaxine, milnacipram, and didesmethylcitalopram. This specific and sensitive method allows management of intoxication and is suitable for the routine determination of antidepressants in forensic investigations.

L37 ANSWER 3 OF 18 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2007432976 EMBASE Full-text
TITLE: Citalopram-induced macropsia [2].
AUTHOR: Ghanizadeh, Ahmad, Dr. (correspondence)
CORPORATE SOURCE: Department of Psychiatry, Shiraz University of Medical Sciences, Hafez Hospital, Shiraz, Iran, Islamic Republic of. ghanizad@sina.tums.ac.ir
SOURCE: Clinical Neuropharmacology, (Jul 2007) Vol. 30, No. 4, pp. 246-247.
Refs: 9
ISSN: 0362-5664 CODEN: CLNEDB
PUBLISHER IDENT.: 00002826200707000000010
COUNTRY: United States
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Sep 2007
Last Updated on STN: 26 Sep 2007

L37 ANSWER 4 OF 18 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 1

ACCESSION NUMBER: 2006:294979 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600290515
TITLE: Enantiomeric screening of racemic citalopram and metabolites in human urine by entangled polymer solution capillary electrophoresis: An innovatory robustness/ruggedness study.
AUTHOR(S): Berzas-Nevado, Juan Jose; Villasenor-LLerena, Maria Jesus [Reprint Author]; Guiberteau-Cabanillas, Carmen; Rodriguez-Robledo, Virginia
CORPORATE SOURCE: Univ Castilla La Mancha, Dept Analyt Chem and Food Technol, E-13071 Ciudad Real, Spain
mjvillas@qata-cr.uclm.es
SOURCE: Electrophoresis, (FEB 2006) Vol. 27, No. 4, Sp. Iss. SI, pp. 905-917.
CODEN: ELCTDN. ISSN: 0173-0835.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 31 May 2006
Last Updated on STN: 31 May 2006

AB Several CE methods have been developed to achieve the chiral separation of citalopram (CIT) and its metabolites demethylcitalopram (DCIT), didemethylcitalopram (DDCIT), and citalopram N-oxide (CIT-NO). All of these compounds were present as racemic mixtures. The best method, which led to the first ever chiral screening of CIT, DCIT, DDCIT, and CIT-NO, involved the use of carboxymethyl-gamma-CD (CM-gamma-CD) and the entangled polymer hydroxypropylmethylcellulose (HPMC) as chiral and selectivity additives, respectively, in the buffer system. In an effort to improve the selectivity and sensitivity of the method, the chemical and instrumental parameters were optimized. The best conditions were short-end anodic hydrodynamic injection (6 s, 0.7 psi); as BGE pH 5, 20 mM phosphate buffer, 0.2% w/v CM-gamma-CD, 0.05% w/v HPMC; voltage of 28 kV with a ramp applied (0.4 s); cartridge temperature of 20 degrees C; detection at 205 nm. In addition, a simple and rapid achiral CE method for the determination of citalopram propionic acid (CIT-PA, the only anionic metabolite of CIT) is also reported for the first time. Prior to the electrophoretic procedure it was necessary to apply an extraction and preconcentration step to obtain analytes from the human urine samples. This was achieved using an optimized SPE process. Moreover, an innovatory experimental and statistical design approach, which involves the simultaneous evaluation of the global robustness and ruggedness effects, was applied. Both of the proposed methods proved to be very useful in the chiral pharmacokinetic screening of CIT and related metabolites in clinical human urine samples.

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ACCESSION NUMBER:	2006138350 EMBASE Full-text
TITLE:	Tolerability and safety of fluvoxamine and other antidepressants.
AUTHOR:	Westenberg, H.G.M.
CORPORATE SOURCE:	Department of Psychiatry, University Medical Centre, Utrecht, Netherlands.
AUTHOR:	Sandner, Claudio, Dr (correspondence)
CORPORATE SOURCE:	Clinigoa - Medical Clinic, Avenida de Goa 12, Amadora, Lisbon, Portugal. claudio.sandner@gmail.com
SOURCE:	International Journal of Clinical Practice, (Apr 2006) Vol. 60, No. 4, pp. 482-491. Refs: 134 ISSN: 1368-5031 E-ISSN: 1742-1241 CODEN: IJCPF9
COUNTRY:	United Kingdom
DOCUMENT TYPE:	Journal; Article
FILE SEGMENT:	030 Clinical and Experimental Pharmacology 032 Psychiatry 037 Drug Literature Index 038 Adverse Reactions Titles 052 Toxicology
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 5 Apr 2006 Last Updated on STN: 5 Apr 2006

AB Selective serotonin [5-hydroxytryptamine (5-HT)] reuptake inhibitors (SSRIs) and the 5-HT noradrenaline reuptake inhibitor, venlafaxine, are mainstays in treatment for depression. The highly specific actions of SSRIs of enhancing serotonergic neurotransmission appears to explain their benefit, while lack of direct actions on other neurotransmitter systems is responsible for their superior safety profile compared with tricyclic antidepressants. Although SSRIs (and venlafaxine) have similar adverse effects, certain differences are emerging. Fluvoxamine may have fewer effects on sexual dysfunction and sleep pattern. SSRIs have a cardiovascular safety profile superior to that of

tricyclic antidepressants for patients with cardiovascular disease; fluvoxamine is safe in patients with cardiovascular disease and in the elderly. A discontinuation syndrome may develop upon abrupt SSRI cessation. SSRIs are more tolerable than tricyclic antidepressants in overdose, and there is no conclusive evidence to suggest that they are associated with an increased risk of suicide. Although the literature suggests that there are no clinically significant differences in efficacy amongst SSRIs, treatment decisions need to be based on considerations such as patient acceptability, response history and toxicity. .COPYRGT. Blackwell Publishing Ltd, 2006.

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ACCESSION NUMBER: 2005521526 EMBASE Full-text
TITLE: The pharmacokinetics of escitalopram after oral and intravenous administration of single and multiple doses to healthy subjects.
AUTHOR: Sogaard, B. (correspondence); Mengel, H.; Larsen, F.
CORPORATE SOURCE: Department of Clinical Pharmacology and Pharmacokinetics, H. Lundbeck A/S, Copenhagen, Denmark.
AUTHOR: Rao, N.
CORPORATE SOURCE: Forest Research Institute, Forest Laboratories, Inc., Jersey City, NJ, United States.
AUTHOR: Sogaard, B. (correspondence)
CORPORATE SOURCE: Department of Clinical Pharmacology, H. Lundbeck A/S, Ottiliavej 7, DK-2500 Copenhagen-Valby, Denmark.
SOURCE: Journal of Clinical Pharmacology, (Dec 2005) Vol. 45, No. 12, pp. 1400-1406.
Refs: 14
ISSN: 0091-2700 CODEN: JCPCBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Dec 2005
Last Updated on STN: 6 Sep 2007

AB The pharmacokinetics of escitalopram (S-citalopram) and its principal metabolite, S-demethylcitalopram (S-DCT), were investigated after intravenous and oral administration to healthy subjects. After intravenous infusion of escitalopram, the mean systemic clearance and volume of distribution were 31 L/h and 1100 L, respectively. After oral administration of single or multiple doses, the absorption was relatively fast, with the maximum observed plasma or serum concentration (C(max)) attained after 3 to 4 hours. The mean half-lives were 27 and 33 hours, respectively; steady state was attained within 10 days. The area under the plasma or serum concentration-time curve from time zero to 24 hours and C(max) was both linear and proportional to the dose. The apparent volume of distribution was around 20 L/kg. Comparison of the systemic and oral clearance implied a high absolute bioavailability. There was no evidence of interconversion from S-citalopram to R-citalopram either in plasma or in urine. Concurrent intake of food had no effect on the pharmacokinetics of escitalopram or its metabolite. All treatments were well tolerated. .COPYRGT.2005 the American College of Clinical Pharmacology.

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ACCESSION NUMBER: 2005198700 EMBASE Full-text
TITLE: Actual driving performance and psychomotor function in healthy subjects after acute and subchronic treatment with escitalopram, mirtazapine, and placebo: A crossover trial.
AUTHOR: Wingen, Marleen (correspondence); Ramaekers, Johannes G.
CORPORATE SOURCE: Experimental Psychopharmacology Unit, Brain and Behaviour Institute, University of Maastricht, Maastricht, Netherlands. m.wingen@psychology.unimaas.nl
AUTHOR: Bothmer, John; Langer, Stefan
CORPORATE SOURCE: Lundbeck GmbH, Hamburg, Germany.
AUTHOR: Wingen, Marleen (correspondence)
CORPORATE SOURCE: Maastricht University, Faculty of Psychology, Department of Neurocognition, P.O. Box 616, 6200 MD Maastricht, Netherlands. m.wingen@psychology.unimaas.nl
SOURCE: Journal of Clinical Psychiatry, (Apr 2005) Vol. 66, No. 4, pp. 436-443.
Refs: 31
ISSN: 0160-6689 CODEN: JCLPDE
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 May 2005
Last Updated on STN: 6 Sep 2007

AB Objective: The effects of escitalopram 10 to 20 mg/day and mirtazapine 30 to 45 mg/day on actual driving and psychomotor performance of 18 healthy subjects were determined in a randomized, double-blind, placebo-controlled, multiple-dose, 3-way crossover trial. Method: Each treatment period lasted for 15 days and was separated from the next period by a washout period of at least 13 days. Subjects received an evening dose of escitalopram 10 mg, mirtazapine 30 mg, or placebo from days 1 to 7 and an evening dose of escitalopram 20 mg, mirtazapine 45 mg, or placebo from days 8 to 15. On days 2, 9, and 16, reflecting acute period, dose increase, and steady state, respectively, the Road Tracking Test was performed. The main parameter was standard deviation of lateral position. Psychomotor performance was also assessed on days 2, 9, and 16 by laboratory computer tasks. Subjective sleep quality was measured with the Groninger Sleep Quality Scale, and mood was measured by visual analogue scales. Results: Treatment differences were apparent during the acute treatment period, in which subjects treated with mirtazapine 30 mg performed less well on the driving test as compared to placebo. The Divided Attention Task results also revealed a significant increase in tracking error after a single dose of mirtazapine 30 mg as compared to placebo. Mirtazapine decreased feelings of alertness and contentedness. Mirtazapine did not affect performance on days 9 and 16 of treatment. Escitalopram did not affect driving, psychomotor performance, or subjective mood throughout treatment. Conclusion: Driving performance, as well as psychomotor functioning, was not affected by escitalopram treatment in healthy subjects. Driving performance was significantly impaired after ingestion of mirtazapine 30 mg during the acute treatment period.

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ACCESSION NUMBER: 2004425296 EMBASE Full-text
TITLE: The chicken serotonin transporter discriminates between

serotonin-selective reuptake inhibitors: A species-scanning mutagenesis study.
AUTHOR: Larsen, Mads Breum; Elfving, Betina; Wiborg, Ove (correspondence)
CORPORATE SOURCE: Laboratory of Molecular Neurobiology, Department of Biological Psychiatry, Aarhus Psychiat. University Hospital, Skovagervej 2, Risskov 8240, Denmark. owiborg@post.tele.dk
SOURCE: Journal of Biological Chemistry, (1 Oct 2004) Vol. 279, No. 40, pp. 42147-42156.
Refs: 44
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Oct 2004
Last Updated on STN: 28 Oct 2004

AB The serotonin transporter (SERT) belongs to a family of sodium chloride-dependent transporters responsible for uptake of amino acids and biogenic amines from extracellular spaces. SERT represents the main pharmacological target in the treatment of several clinical conditions, including depression and anxiety. Serotonin-selective reuptake inhibitors and tricyclic antidepressants are the most predominantly prescribed drugs in the treatment of depression. In addition to antidepressants also psychostimulants, like cocaine and amphetamines, are important SERT antagonists. In the present study, we report the cloning and characterization of chicken SERT. Although the uptake kinetic was very similar to human SERT, the pharmacological profiles differed considerably for the two species. We find that chicken SERT is capable of discriminating between different serotonin-selective reuptake inhibitors; thus, the potency of S-citalopram and paroxetine is reduced more than 40-fold. A cross-species chimera strategy was undertaken and followed by species-scanning mutagenesis. Differences in pharmacological profiles were tracked to amino acid residues 169, 172, and 586 in human SERT. Structure-activity studies on structurally related compounds indicated that species divergences in drug sensitivity between human and chicken SERT were arising from differences in coordination or recognition of an important aminomethyl pharmacophoric substructure, which is shared by all high affinity antidepressants. Consequently, we suggest that Ala(169) and Ile(172) of human SERT are important residues in sensing the N-methylation state of SERT antagonists.

L37 ANSWER 9 OF 18 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005026876 EMBASE Full-text
TITLE: Simultaneous chiral analytes of multiple analytes: Case studies, implications and method development considerations.
AUTHOR: Srinivas, Nuggehally R. (correspondence)
CORPORATE SOURCE: Drug Development, Discovery Research, Dr. Reddy's Laboratories, Bollaram Road, Miyapur, Hyderabad 500 049, India. nrsrinivas@drreddys.com
SOURCE: Biomedical Chromatography, (Dec 2004) Vol. 18, No. 10, pp. 759-784.
Refs: 65
ISSN: 0269-3879 CODEN: BICHE2
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 022 Human Genetics
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
049 Forensic Science Abstracts
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jan 2005
Last Updated on STN: 27 Jan 2005

AB The field of chiral separations had a modest beginning some two decades ago. However, due to rapid technological advancement coupled with simultaneous availability of innovative chiral stationary phases and novel chiral derivatization. agents, the field of chiral separations has now totally outpaced many other separation fields. Keeping pace with rapid changes in the field of chiral separations, investigators continue to add stereoselective pharmacokinetic, pharmacodynamic, pharmacologic and toxicological data of new and/or marketed racemic compounds to the literature. Examination of the evolution of chiral separations suggests that in the beginning many investigators attempted to separate and quantify a single pair of enantiomers, adopting either direct (separation made on a chiral stationary phase) or indirect (separation made following precolumn conversion of enantiomers to corresponding diastereomers) approaches. However, more recent trends in chiral separations suggest that investigators are attempting to separate and quantify multiple pairs of enantiomers with available technologies. Added to this, some interesting trends have been observed in many of the recently reported chiral applications, including preferences regarding internal standard selection, mobile phase contents and composition, sorting out issues with mass spectrometric detection, determination of elution order, analytical manipulations of metabolite(s) without reference standards and addressing some specificity-related issues. This review mainly focuses on chiral separations involving multiple chiral analytes and attempts to justify the need for such chiral separations involving multiple analytes. In this context, several cases studies are described on the utility and applicability of such chiral separations under discrete headings to provide an account to the readership on the implications of such tasks. The topics of case studies covered in this review include: (a) therapy markers - differentiation from drug abuse and/or applicability in forensics; (b) role in pharmacogenetic/polymorphic evaluation; (c) monitoring and understaning the role of parent and active metabolite(s) in clinical and preclinical investigations; (d) exploration on the pharmacokinetic utility of an active chiral metabolite vis-a-vis the racemic parent moiety; (e) understanding the chirality play in delineating peculiar toxic effects; (f) exploration of chiral inversion phenomenon, and understanding the role of stereoselective metabolism. For the further benefit of readership, some select examples (n = 19) of the separation of multiple chiral analytes with appropriate information on chromatography, detection system, validation parameters and applicable conclusion are also provided. Finally, the review covers some useful considerations for method development involving multiple chiral analytes. Copyright .COPYRGT. 2004 John Wiley & Sons, Ltd.

L37 ANSWER 10 OF 18 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004126908 EMBASE Full-text
TITLE: Enantioselective Analysis of Citalopram and its Metabolites in Postmortem Blood and Genotyping for CYD2D6 and CYP2C19.
AUTHOR: Holmgren, Per (correspondence); Ahlner, Johan

CORPORATE SOURCE: Department of Forensic Chemistry, Faculty of Health Science, Linkoping University, S-581 85 Linkoping, Sweden. per.holmgren@rmv.se
AUTHOR: Carlsson, Bjorn; Zackrisson, Anna-Lena
CORPORATE SOURCE: Department of Clinical Pharmacology, Faculty of Health Science, Linkoping University, S-581 85 Linkoping, Sweden.
AUTHOR: Lindblom, Berti
CORPORATE SOURCE: Department of Forensic Genetics, Faculty of Health Science, Linkoping University, S-581 85 Linkoping, Sweden.
AUTHOR: Dahl, Marja-Liisa
CORPORATE SOURCE: Department of Medical Sciences, Clinical Pharmacology, University Hospital, S-751 85 Uppsala, Sweden.
AUTHOR: Scordo, Maria Gabriella
CORPORATE SOURCE: Dept. of Med. Lab. Sci. and Technol., Karolinska Institutet, University Hospital, S-141 86 Stockholm, Sweden.
AUTHOR: Druid, Henrik
CORPORATE SOURCE: National Board of Forensic Medicine, Department of Forensic Medicine, Karolinska Institutet, Solna, Sweden .
SOURCE: Journal of Analytical Toxicology, (Mar 2004) Vol. 28, No. 2, pp. 94-104.
Refs: 37
ISSN: 0146-4760 CODEN: JATOD3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
032 Psychiatry
037 Drug Literature Index
049 Forensic Science Abstracts
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Apr 2004
Last Updated on STN: 12 Apr 2004

AB Citalopram, a selective serotonin reuptake inhibitor, is one of the most commonly found drugs in Swedish forensic autopsy cases. Citalopram is a racemic drug with 50:50 of the S- and R-enantiomers. Enantioselective analysis of citalopram and its metabolites desmethylcitalopram and didesmethylcitalopram were performed in femoral blood from 53 autopsy cases by a chiral high-performance liquid chromatography (HPLC) method. The mean (± standard deviation) S/R ratio for citalopram was 0.67 ± 0.25 and for desmethylcitalopram, 0.68 ± 0.20. We found increasing S/R ratios with increasing concentrations of citalopram. We also found that high citalopram S/R ratios were associated with a high parent drug-to-metabolite ratio and may be an indicator of recent intake. Citalopram is metabolized by cytochrome P450 (CYP) 3A4, 2C19, and 2D6. Genotyping for the polymorphic CYP2C19 and CYP2D6 revealed no poor metabolizers regarding CYP2C19 and only 2 (3.8%) poor metabolizers regarding CYP2D6. The presence of drugs metabolized by and/or inhibiting these enzymes in several of the cases suggests that such pharmacokinetic interactions are a more important (practical) problem than metabolic deficiency. Enantioselective analysis of citalopram and its metabolites can provide additional information when interpreting forensic toxicology results and might be a necessity in the future.

L37 ANSWER 11 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2003366140 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 12900873
TITLE: Enantiomeric separation of citalopram and its metabolites by capillary electrophoresis.
AUTHOR: Mandrioli Roberto; Fanali Salvatore; Pucci Vincenzo; Raggi Maria A
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Bologna, Via Belmeloro 6, I-40126 Bologna, Italy.
SOURCE: Electrophoresis, (2003 Aug) Vol. 24, No. 15, pp. 2608-16.
Journal code: 8204476. ISSN: 0173-0835.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 18 Jun 2004
Entered Medline: 17 Jun 2004

AB A simple and fast capillary electrophoretic method has been developed for the enantioselective separation of citalopram and its main metabolites, namely N-desmethylcitalopram and N,N-didesmethylcitalopram, using beta-cyclodextrin (beta-CD) sulfate as the chiral selector. For method optimisation several parameters were investigated, such as CD and buffer concentration, buffer pH, and capillary temperature. Baseline enantioseparation of the racemic compounds was achieved in less than 6 min using a fused-silica capillary, filled with a background electrolyte consisting of a 35 mM phosphate buffer at pH 2.5 supplemented with 1% w/v beta-CD sulfate and 0.05% w/v beta-CD at 25 degrees C and applying a voltage of -20 kV. A fast separation method for citalopram was also optimized and applied to the analysis of pharmaceutical formulations. Racemic citalopram was resolved in its enantiomers in less than 1.5 min using short-end injection (8.5 cm, effective length) running the experiments in a background electrolyte composed of a 25 mM citrate buffer at pH 5.5 and 0.04% w/v beta-CD sulfate at a temperature of 10 degrees C.

L37 ANSWER 12 OF 18 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003395640 EMBASE Full-text
TITLE: Metabolism of citalopram enantiomers in CYP2C19/CYP2D6 phenotyped panels of healthy Swedes.
AUTHOR: Herrlin, Karin, Dr. (correspondence); Yasui-Furukori, Norio; Tybring, Gunnel; Widen, Jolanta; Gustafsson, Lars L.; Bertilsson, Leif
CORPORATE SOURCE: Department of Medicine Laboratory, Karolinska Institutet, Huddinge University Hospital, Huddinge, Sweden. karin.herrlin@labtek.ki.se
AUTHOR: Herrlin, Karin, Dr. (correspondence)
CORPORATE SOURCE: c/o Leif Bertilsson, Division of Clinical Pharmacology, Huddinge University Hospital, S-141 86 Huddinge, Sweden . karin.herrlin@labtek.ki.se
SOURCE: British Journal of Clinical Pharmacology, (1 Oct 2003) Vol. 56, No. 4, pp. 415-421.
Refs: 27
ISSN: 0306-5251 CODEN: BCPHBM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Oct 2003
Last Updated on STN: 16 Oct 2003

AB Aims: To investigate pharmacokinetics of the enantiomers of citalopram (CT) and its metabolites desmethylcitalopram (DCT) and didesmethylcitalopram (DDCT) in Swedish healthy volunteers in relation to CYP2C19 and CYP2D6 geno- and phenotypes. Methods: Racemic CT was given for seven days to panels with different genotypes and the following mephenytoin (Me) and debrisoquine (De) hydroxylation phenotypes: EM(De)/EM(Me), PM (De)/EM(Me), EM(De)/PM(Me) (n=6 in all groups), and one PM(De)/PM(Me) subject. Blood sampling was carried out during day 7, and all urine was collected for 12 h after the last dose of CT. Results: The AUC of S-CT was significantly higher in the EM (De)/PM(Me) panel compared to the EM(De)/EM (Me) and PM(De)/EM(Me) panels ($P < 0.05$), whereas the AUC of R-CT did not differ between the panels. Similar differences, although they did not reach statistical significance, were noted for S-DCT and R-DCT. The enantiomers of DDCT were not quantifiable in PM(De) and there was no difference in DDCT enantiomer concentrations between the other two panels. A PM(De)/PM(Me) subject stopped taking CT after five days due to severe adverse effects. Based on two time points, this subject had a very long CT half-life of 95 h. The value of 1.0 for the S/R ratio of the CT trough in this subject was similar to the mean S/R CT trough ratio of the EM(De)/PM(Me) panel, but higher than the S/R CT ratio of the EM(De)/EM(Me) panel (0.56; 95% CI 0.49-0.63) and the PM (De)/EM(Me) panel (0.44; 95% CI 0.31-0.57). Thus the latter two phenotypes eliminated S-CT more rapidly via CYP2C19. An adverse effect described as an 'alcohol hangover' feeling was reported by one subject from each of the three panels. These individuals had the highest concentrations of both CT enantiomers. Conclusions: The AUC of S-, but not R-(CT) was found to be significantly higher in PM of mephenytoin compared to EMs, PMs may need a lower dosage of CT.

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ACCESSION NUMBER: 2003319637 EMBASE Full-text
TITLE: Pharmacokinetic and pharmacodynamic evaluation of the inhibition of alprazolam by citalopram and fluoxetine.
AUTHOR: Hall, Judith; Naranjo, Claudio A., Dr. (correspondence); Sproule, Beth A.; Herrmann, Nathan
CORPORATE SOURCE: Psychopharmacology Research Program, Sunnybrook/Women's Coll. Hlth. S. C., University of Toronto, 2075 Bayview Avenue, Toronto, Ont. M4N 3M5, Canada. claudio.naranjo@utoronto.ca
AUTHOR: Hall, Judith; Naranjo, Claudio A., Dr. (correspondence)
CORPORATE SOURCE: Department of Pharmacology, University of Toronto, Toronto, Ont., Canada. claudio.naranjo@utoronto.ca
AUTHOR: Naranjo, Claudio A., Dr. (correspondence); Herrmann, Nathan
CORPORATE SOURCE: Department of Medicine, University of Toronto, Toronto, Ont., Canada. claudio.naranjo@utoronto.ca
AUTHOR: Sproule, Beth A.
CORPORATE SOURCE: Faculty of Pharmacy, University of Toronto, Toronto, Ont., Canada.
AUTHOR: Herrmann, Nathan
CORPORATE SOURCE: Department of Psychiatry, University of Toronto, Toronto, Ont., Canada.
SOURCE: Journal of Clinical Psychopharmacology, (Aug 2003) Vol. 23, No. 4, pp. 349-357.
Refs: 33
ISSN: 0271-0749 CODEN: JCPYDR

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Aug 2003
Last Updated on STN: 28 Aug 2003

AB The selective serotonin reuptake inhibitor antidepressant fluoxetine inhibits alprazolam metabolism in vivo by inhibition of the cytochrome P450 3A4 enzyme. Citalopram is a selective serotonin reuptake inhibitor antidepressant that has not yet been fully evaluated with respect to its potential for cytochrome P450 3A4-mediated drug interactions in vivo. Building on the existing in vitro and in vivo evidence that suggest a minimal effect of citalopram on cytochrome P450 3A4, we hypothesized that therapeutic doses of citalopram (20 mg/d), as compared with fluoxetine (20 mg/d), would cause less impairment in the metabolism of the probe drug alprazolam (1 mg) through inhibition of the cytochrome P450 3A4 isozyme as measured by pharmacokinetic and pharmacodynamic parameters in vivo. We found that fluoxetine prolonged the half-life of alprazolam by 16% and increased the area under the curve 0-∞ of alprazolam by 32%, while citalopram did not affect these parameters, although the time of maximum concentration of alprazolam was prolonged by 30 minutes after citalopram administration. Neither selective serotonin reuptake inhibitor significantly affected the pharmacodynamic profile of alprazolam. This experiment suggests differential effects by citalopram and fluoxetine on alprazolam kinetics.

L37 ANSWER 14 OF 18 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2002348817 EMBASE Full-text
TITLE: Enantiomers' potential in psychopharmacology - A critical analysis with special emphasis on the antidepressant escitalopram.
AUTHOR: Baumann, Pierre (correspondence); Zullino, Daniele F; Eap, Chin B
CORPORATE SOURCE: Departement Universitaire de Psychiatrie Adulte, Unite de Biochimie et Psychopharmacologie Clinique, Hopitalde Cery, CH-1008 Prilly-Lausanne, Switzerland. pierre.baumann@inst.hospvd.ch
AUTHOR: Baumann, Pierre (correspondence)
CORPORATE SOURCE: Dept. Univ. de Psychiatrie Adulte, U. Biochim./Psychopharmacol. Clin., Hopitalde Cery, CH-1008 Prilly-Lausanne, Switzerland. pierre.baumann@inst.hospvd.ch
SOURCE: European Neuropsychopharmacology, (Oct 2002) Vol. 12, No. 5, pp. 433-444.
Refs: 78
ISSN: 0924-977X CODEN: EURNE8
PUBLISHER IDENT.: S 0924-977X(02)00051-2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
008 Neurology and Neurosurgery
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 17 Oct 2002
Last Updated on STN: 17 Oct 2002

AB Stereochemistry is now influencing most areas of pharmacotherapy, with a growing awareness in the field of psychiatry and, more specifically, depression. This is due to the fact that the enantiomers of many chiral drugs may have distinct pharmacological, pharmacokinetic and/or pharmacogenetic profiles. Consequently, in some instances there may be an advantage in using a single enantiomer over the racemic form - thus providing a basis for the development of new therapeutic agents, as well as the potential to improve current treatments. This review highlights some of the potential advantages and disadvantages that using single enantiomers might offer. The principles are exemplified through reference to the stereoselective properties of several established chiral psychotropic drugs, including thioridazine, methadone, trimipramine, mianserin, mirtazapine, fluoxetine and citalopram. Emphasis is given to the treatment of depression and how the potential of one pure enantiomer - escitalopram, the S-enantiomer of the selective serotonin reuptake inhibitor citalopram - appears to be fulfilling its preclinical promise in the clinic. .COPYRGT. 2002 Elsevier Science B.V./ECNP. All rights reserved.

L37 ANSWER 15 OF 18 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001121289 EMBASE Full-text
TITLE: Optimization and characterization of the chiral separation of citalopram and its demethylated metabolites by response-surface methodology.
AUTHOR: Carlsson, B. (correspondence); Norlander, B.
CORPORATE SOURCE: Division of Clinical Pharmacology, Department of Medicine and Care, Linkoping University, 581 85 Linkoping, Sweden. bjorn.carlsson@lio.se
AUTHOR: Carlsson, B. (correspondence)
CORPORATE SOURCE: Division of Clinical Pharmacology, Department of Medicine, Linkoping University, 58185 Linkoping, Sweden . bjorn.carlsson@lio.se
SOURCE: Chromatographia, (2001) Vol. 53, No. 5-6, pp. 266-272.
Refs: 29
ISSN: 0009-5893 CODEN: CHRGB7
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Apr 2001
Last Updated on STN: 19 Apr 2001

AB Response-surface modelling and sequential optimization have been used for optimization and characterization of the separation of the enantiomers of citalopram, desmethylcitalopram, and didesmethylcitalopram on an acetylated β-cyclodextrin column. In the model chosen the separation conditions mobile phase methanol content, buffer concentration, column temperature, and pH were varied to investigate their influence on the chromatography. It was found that what is good for selectivity within an enantiomer pair is bad for selectivity between enantiomer pairs. Because within-pair and between-pair selectivity does not reach its optimum at the same conditions, a middle course approach has to be followed. Use of an experimental design for this investigation enabled understanding of the mechanisms of within- and between-

pair separation for citalopram, desmethylcitalopram, and didesmethylcitalopram. Sequential optimization can be a quicker means of optimizing a chromatographic separation; response-surface modelling, in addition to enabling optimization of the chromatographic process, also serves as a tool for learning more about the separation mechanism.

L37 ANSWER 16 OF 18 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:68416 BIOSIS Full-text
DOCUMENT NUMBER: PREV200000068416
TITLE: Simultaneous determination of citalopram, fluoxetine, paroxetine and their metabolites in plasma and whole blood by high-performance liquid chromatography with ultraviolet and fluorescence detection.
AUTHOR(S): Kristoffersen, L. [Reprint author]; Bugge, A.; Lundanes, E.; Slordal, L.
CORPORATE SOURCE: National Institute of Forensic Toxicology, N-0105, Oslo, Norway
SOURCE: Journal of Chromatography B, (Nov. 12, 1999) Vol. 734, No. 2, pp. 229-246. print.
CODEN: JCBADL. ISSN: 0378-4347.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Feb 2000
Last Updated on STN: 3 Jan 2002

AB A method for the simultaneous determination of the three selective serotonin reuptake inhibitors (SSRIs) citalopram, fluoxetine, paroxetine and their metabolites in whole blood and plasma was developed. Sample clean-up and separation were achieved using a solid-phase extraction method with C8 non-endcapped columns followed by reversed-phase high-performance liquid chromatography with fluorescence and ultraviolet detection. The robustness of the solid-phase extraction method was tested for citalopram, fluoxetine, paroxetine, Cl-citalopram and the internal standard, protriptyline, using a fractional factorial design with nine factors at two levels. The fractional factorial design showed two significant effects for paroxetine in whole blood. The robustness testing for citalopram, fluoxetine, Cl-citalopram and the internal standard revealed no significant main effects in whole blood and plasma. The optimization and the robustness of the high-performance liquid chromatographic separation were investigated with regard to pH and relative amount of acetonitrile in the mobile phase by a central composite design circumscribed. No alteration in the elution order and no significant change in resolution for a deviation of +-1% acetonitrile and +-0.3 pH units from the specified conditions were observed. The method was validated for the concentration range 0.050-5.0 mumol/l with fluorescence detection and 0.12-5.0 mumol/l with ultraviolet detection. The limits of quantitation were 0.025 mumol/l for citalopram and paroxetine, 0.050 mumol/l for desmethyl citalopram, di-desmethyl citalopram and citalopram-N-oxide, 0.12 mumol/l for the paroxetine metabolites by fluorescence detection, and 0.10 mumol/l for fluoxetine and norfluoxetine by ultraviolet detection. Relative standard deviations for the within-day and between-day precision were in the ranges 1.4-10.6% and 3.1-20.3%, respectively. Recoveries were in the 63-114% range for citalopram, fluoxetine and paroxetine, and in the 38-95% range for the metabolites. The method has been used for the analysis of whole blood and plasma samples from SSRI-exposed patients and forensic cases.

L37 ANSWER 17 OF 18 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1996106556 EMBASE Full-text

TITLE: Neuroendocrine effects of a 20-mg citalopram infusion in healthy males. A placebo-controlled evaluation of citalopram as 5-HT function probe.
AUTHOR: Seifritz, E., Dr. (correspondence); Baumann, P.; Muller, M.J.; Annen, O.; Amey, M.; Hemmeter, U.; Hatzinger, M.; Chardon, F.; Holsboer-Trachsler, E.
CORPORATE SOURCE: Psychiatry Service, Veterans Affairs Medical Center, 3350 La Jolla Village Drive, San Diego, CA 92161, United States.
SOURCE: Neuropsychopharmacology, (1996) Vol. 14, No. 4, pp. 253-263.
ISSN: 0893-133X CODEN: NEROEW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 13 May 1996
Last Updated on STN: 13 May 1996

AB Pharmacokinetic measurements, neuroendocrine responses, and side effects profiles of intravenous infusions of 20 mg citalopram over 30 minutes during the early afternoon have been studied. Eight healthy male volunteers were enrolled in a placebo-(saline) controlled, single-blind, cross-over protocol. Plasma concentrations of the parent compound showed a double exponential decay. Demethyl and didemethyl metabolites were not detectable, but low concentrations of the propionic acid derivative of citalopram were found. Determination of the citalopram enantiomers yielded a balanced S(+)/R(-) ratio of 0.9 to 1.2. The endocrine response to the drug was characterized by significant increases in plasma prolactin and cortisol. Except for one subject, who developed pronounced side effects, human growth hormone showed a surge following saline that was inhibited following citalopram. Rectal temperature and heart rate were not affected and tolerability was favorable. Because of citalopram's extremely high selectivity for the presynaptic 5-hydroxytryptamine nerve terminals, the present data suggest that it might be a promising tool for the investigation of serotonergic function in the human brain in vivo.

L37 ANSWER 18 OF 18 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1995318803 EMBASE Full-text
TITLE: Determination of the enantiomers of citalopram, its demethylated and propionic acid metabolites in human plasma by chiral HPLC.
AUTHOR: Rochat, B.; Amey, M.; Van Gelderen, H.; Testa, B.; Baumann, P., Dr. (correspondence)
CORPORATE SOURCE: DUPA, Hopital de Cery, CH-1008 Prilly-Laussane, Switzerland.
SOURCE: Chirality, (1995) Vol. 7, No. 6, pp. 389-395.
ISSN: 0899-0042 CODEN: CHRLEP
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 21 Nov 1995

Last Updated on STN: 21 Nov 1995

AB A stereoselective HPLC assay has been developed to analyze the enantiomers of citalopram and of its three main metabolites in plasma after their separation on a Chiracel OD column. Using a fluorescence detector, the limit of quantification in plasma samples was 15, 4, 5, and 2 ng/ml for the enantiomers of citalopram (CIT), desmethyleitalopram (DCIT), didesmethylcitalopram (DDCIT), and for the citalopram propionic acid derivative (CIT-PROP), respectively. Except for CIT, all metabolites were derivatized with achiral reagents. Identification of the enantiomers was realized with an optical rotation detector which showed that the enantiomers inert their rotation depending on the polarity and nature of the solvent. Under varying condition, a racemization study has shown that the pure enantiomers of CIT and its demethylated metabolites are configurationally stable. Preliminary results obtained with five patients treated with CIT show a means S/R ratio of 0.7 for both CIT and its active metabolite DCIT and of 3.6 for CIT PROP in plasma. This suggests that the pharmacologically relevant (+)-(S)-isomers of CIT and DCIT could be preferentially and stereoselectively metabolized to CIT-PROP.

FILE 'MARPAT' ENTERED AT 16:38:14 ON 05 MAR 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE CONTENT: 1961-PRESENT VOL 150 ISS 8 (20090227/ED)

MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

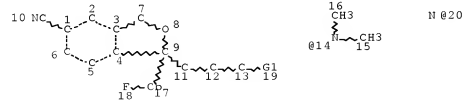
MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US 20090018200 15 JAN 2009
DE 102007040251 08 JAN 2009
EP 2014745 14 JAN 2009
JP 2009007348 15 JAN 2009
WO 2009012656 29 JAN 2009
GB 2450771 07 JAN 2009
FR 2918372 09 JAN 2009
RU 2342397 27 DEC 2008
CA 2631186 19 DEC 2008

Expanded G-group definition display now available.

The new MARPAT User Guide is now available at:
http://www.cas.org/support/stngen/stndoc/marpat.html.

L12 STR



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CONNECT IS X2  RC AT  12
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GGCAT   IS MCY  UNS  AT  17
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  20

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

L14          20 SEA FILE=MARPAT SSS FUL L12 (MODIFIED ATTRIBUTES)
L38             STR
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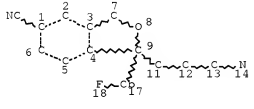


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NUMBER OF NODES IS  16

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

L39           9 SEA FILE=MARPAT SUB=L14 SSS FUL L38 (MODIFIED ATTRIBUTES)

100.0% PROCESSED      20 ITERATIONS                              9 ANSWERS
SEARCH TIME: 00.00.01


     FILE 'CAPLUS' ENTERED AT 16:40:15 ON 05 MAR 2009
L40           9 SEA ABB=ON  PLU=ON  L39
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L41             2 SEA ABB=ON  PLU=ON  L40 NOT (L8 OR L20 OR L30)
L42             0 SEA ABB=ON  PLU=ON  L41 AND (OPTIAL? OR CHIRAL OR ENRIOMER?
                  OR RESOLUT? OR METHYLAT?)
L43             2 SEA ABB=ON  PLU=ON  L41 AND (RACT OR RCT)/RL

     FILE 'MARPAT' ENTERED AT 16:41:04 ON 05 MAR 2009
L44             2 SEA ABB=ON  PLU=ON  L43
L45             2 SEA ABB=ON  PLU=ON  L44 NOT L21

L45  ANSWER 1 OF 2  MARPAT  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         129:81750  MARPAT  Full-text
TITLE:                    Preparation of
                          N-piperazinoalkyl-ω-aminoalkanamides as
                          5-HT1A receptor antagonists and serotonin reuptake
                          inhibitors
INVENTOR(S):              Halazy, Serge; Perez, Michel
PATENT ASSIGNEE(S):       Pierre Fabre Medicament, Fr.
SOURCE:                   Fr. Demande, 28 pp.
                          CODEN: FRXXBL
DOCUMENT TYPE:            Patent
LANGUAGE:                 French
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     FR 2756283         A1   19980529       FR 1996-14524    19961127
     WO 9823590         A1   19980604       WO 1997-FR2139   19971127
         W:  AU, BR, CA, CN, JP, KR, MX, NZ, US
         RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE
     AU 9874101         A    19980622       AU 1998-74101    19971127
PRIORITY APPLN. INFO.:                     FR 1996-14524    19961127
                                           WO 1997-FR2139   19971127
OTHER SOURCE(S):          CASREACT 129:81750
GI
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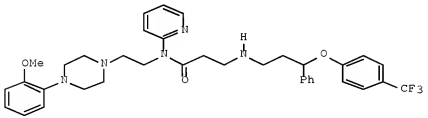

II

AB RZ1(CH2)nCHR4Z2COZNR1R2 (Z1 = piperazine-1,4-diyl)[I; R = (un)substituted (hetero)aryl; R1 = H or (ar)alkyl; R2 = e.g., CH2CH2CHPhOC6H4(CF3)-4, CH2CH2ON:C[(CH2)4OMe]C6H4(CF3)-4, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthyl, etc.; NR1R2 = aryl(oxy)(alkyl)piperidino or -morpholino; Z = (oxy or imino)(phenylene-interrupted)alkylene; Z2 = CHR3 or NR3; R3,R4 = H or (hetero)aryl; n = 0-3] were prepared as 5-HT1A receptor antagonists and serotonin reuptake inhibitors (no data). Thus, 2-(MeO)C6H4Z1CH2CH2NHR3 (R3 =

2-pyridyl; Z1 = piperazine-1,4-diyl) was amidated by ClCOCH:CH2 and the product subjected to Michael addition by H2NCH2CH2CHPhOC6H4(CF3)-4 to give title compound II.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 2 OF 2 MARPAT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 129:81573 MARPAT Full-text
TITLE: Preparation of 1-aryloxyalkyl-2-aminoethanols as 5-HT1A receptor antagonists and serotonin reuptake inhibitors
INVENTOR(S): Halazy, Serge; Perez, Michel
PATENT ASSIGNEE(S): Pierre Fabre Medicament, Fr.
SOURCE: Fr. Demande, 33 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2756286	A1	19980529	FR 1996-14523	19961127
WO 9823586	A1	19980604	WO 1997-FR2138	19971127
W: AU, BR, CA, CN, JP, KR, MX, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9874100	A	19980622	AU 1998-74100	19971127

PRIORITY APPLN. INFO.: FR 1996-14523 19961127
WO 1997-FR2138 19971127
OTHER SOURCE(S): CASREACT 129:81573
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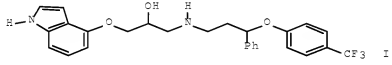

AB RO(CH2)nCH(OH)CH2NR1R2 [R = (un)substituted (hetero)aryl; R1 = H or (ar)alkyl; R2 = ZR3; R3 = e.g., CH2CH2CHPhOC6H4(CF3)-4, CH2CH2ON:C[(CH2)4OMe]C6H4(CF3)-4, etc.; Z = bond, (N-substituted)(phenylene-interrupted)alkyleneimino, etc.; n = 1-4] were prepared as 5-HT1A receptor antagonists and serotonin reuptake inhibitors (no data). Thus, 4-(oxiranylmethoxy)indole was condensed with H2NCH2CH2CHPhOC6H4(CF3)-4 to give title compound I.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

FILE 'REGISTRY' ENTERED AT 16:42:16 ON 05 MAR 2009
E ESCITALOPRAM/CN 5
L46 2 S E3-4

Text – Claim 1 named compd.

FILE 'CAPLUS' ENTERED AT 16:42:44 ON 05 MAR 2009

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L47        3512 S L46 OR ESCITALOPRAM OR CITALOPRAM OR LEXAPRO
L48           5 S L47 AND L6
L49           1 S L48 NOT (L8 OR L20 OR L30 OR L43)

L49  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2009 ACS on STN
ED   Entered STN:  20 Sep 2006
ACCESSION NUMBER:         2006:969618  CAPLUS  Full-text
DOCUMENT NUMBER:          145:356520
TITLE:                    Process for preparation of
                          4-[4-dimethylamino-1-(4-fluorophenyl)-1-hydroxybut
                          yl]-3-hydroxymethylbenzonitrile hydrobromide as
                          citalopram intermediate
INVENTOR(S):              Gao, Rong
PATENT ASSIGNEE(S):       Peop. Rep. China
SOURCE:                   Faming Zhuanli Shenqing Gongkai Shuomingshu, 12pp.
                          CODEN: CNXXEV
DOCUMENT TYPE:            Patent
LANGUAGE:                 Chinese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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     CN 1830952           A     20060913    CN 2006-10038201       20060210
PRIORITY APPLN. INFO.:                     CN 2006-10038201       20060210

OTHER SOURCE(S):          CASREACT 145:356520
AB   This invention provides a process for the preparation of 4-[4-dimethylamino-1-
     (4-fluorophenyl)-1-hydroxybutyl]-3- hydroxymethylbenzonitrile monohydrobromide
     as intermediate for citalopram.  The 1-bromo-4-fluorobenzene refluxed with
     magnesium in THF, followed by reacting with 5-cyanophthalide and the addition
     of Grignard reagent from 3-chloro-N,N-dimethyl-1-propanamine (preparation
     given) to give the title compound in high yield with 99% purity.

     (FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS' ENTERED  AT
     16:44:20 ON 05 MAR 2009)
L50           1 S L48

L50  ANSWER 1 OF 1  WPIX COPYRIGHT 2009       THOMSON REUTERS on STN
ACCESSION NUMBER:     2005-372326 [38]   WPIX
DOC. NO. CPI:         C2006-157739 [52]
TITLE:                Preparation of escitalopram involves
                      reacting didesmethylcitalopram with enantiomerically
                      pure acid, or reacting racemic citalopram
                      with an enantiomerically pure acid, followed by base
                      hydrolysis and methylation
DERWENT CLASS:        B02
INVENTOR:             CHALAMALA S R; CHANDRASHEKAR E R R; ELATI C R;
                      GANGULA S; GOVINDAN S; JAYANTILAL V P; KOLLA N; KUMAR
                      K N; MADDIPATLA M; MATHAD V T; MATHAD V T F N; RAO C
                      S; REDDY G M; REDDY V V; SHANMUGAM G; SUNDARAM V;
                      SUNDARAM V P N; THIPPANNACHAR M V; VENKATARAMAN S;
                      VENKAVALA P J; ELATI R C; KOLLA N K
PATENT ASSIGNEE:      (REDD-N) REDDY'S LAB LTD
COUNTRY COUNT:        107

PATENT INFO ABBR.:

     PATENT NO      KIND DATE     WEEK     LA  PG          MAIN IPC
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WO 2005047274 A1 20050526 (200538)* EN 42[0]
EP 1706394 A1 20061004 (200665) EN
IN 2004CH00370 I4 20070223 (200729) EN
IN 2006CN02934 P4 20070608 (200748) EN

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005047274 A1		WO 2004-US38490	20041112
IN 2004CH00370 I4		IN 2004-CH370	20040422
EP 1706394 A1		EP 2004-811264	20041112
EP 1706394 A1		WO 2004-US38490	20041112
IN 2006CN02934 P4		WO 2004-US38490	20041212
IN 2006CN02934 P4		IN 2006-CN2934	20060809

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1706394	A1	Based on	WO 2005047274 A

PRIORITY APPLN. INFO: US 2004-598725P 20040804
IN 2003-CH924 20031112
IN 2004-CH370 20040422
IN 2006-CN2934 20060809

AN 2005-372326 [38] WPIX

AB WO 2005047274 A1 UPAB: 20051222

NOVELTY - Preparation of escitalopram involves: (a) reacting 5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran with 3-chloropropylamine in presence of a base; (b) reacting obtained didesmethylcitalopram with enantiomerically pure acid;

(c) hydrolysing using a base;

(d) methylating; and

(e) recovering the product.

DETAILED DESCRIPTION - Preparation of escitalopram involves:

(A) method (I) comprising:

(a) reacting 5-cyano-1-(4-fluorophenyl)-1,3- dihydroisobenzofuran with 3-chloropropylamine in presence of a base;

(b) reacting the obtained 5-cyano-1-(4-fluorophenyl)-1-aminopropyl-1,3-dihydroisobenzofuran (didesmethylcitalopram) (i) with an enantiomerically pure acid; (c) hydrolyzing the product of step (b) using base; (d) methylating the product recovered from step (c); and (e) recovering escitalopram; (B) method (II) comprising steps (b) - (e) as above; or (C) method (III) comprising: (a1) reacting racemic citalopram with an enantiomerically pure acid; (b1) hydrolyzing the product of step (a1) using a base; and step (e) as above.

ACTIVITY - None given.

MECHANISM OF ACTION - None given.

USE - For preparation of escitalopram (claimed).

ADVANTAGE - The method is cost effective, does not involve the use of hazardous chemicals such as cyanide as associated in the prior art and is industrially feasible. The recovered escitalopram contains N-(3-(5-cyano-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-1- yl)propyl)formamide (less than 0.2, preferably less than 0.01) weight%.

FILE 'CASREACT' ENTERED AT 16:45:03 ON 05 MAR 2009
L51 22 S L46/PRO
L52 1 S L51 AND L5

L52 ANSWER 1 OF 1 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 142:481937 CASREACT Full-text
TITLE: Preparation of enantiomerically enriched escitalopram
INVENTOR(S): Sundaram, Venkataraman; Mathad, Vijayavitthal Thippannachar; Venkavala, Pravinachandra Jayanthilal; Elati, Chandrashekar Ravirama; Kolla, Naveenkumar; Govindan, Shanmugam; Chalamala, Subrahmanyeshwara Rao; Gangula, Srinivas
PATENT ASSIGNEE(S): Reddy's Laboratories, Inc., USA; Reddy's Laboratories Ltd.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005047274	A1	20050526	WO 2004-US38490	20041112
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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CA 2575975	A1	20050526	CA 2004-2575975	20041112
EP 1706394	A1	20061004	EP 2004-811264	20041112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
IN 2006CN02934	A	20070608	IN 2006-CN2934	20060809
US 20090018351	A1	20090115	US 2007-595794	20070130
PRIORITY APPLN. INFO.:			IN 2003-CH924	20031112
			IN 2004-CH370	20040422
			US 2004-598725P	20040804
			WO 2004-US38490	20041112

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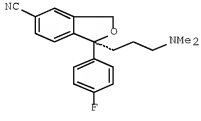
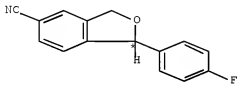


I

AB A process is disclosed for the preparation of enantiomerically enriched escitalopram. The process is comprised of: i. reacting 5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran with 3-chloropropylamine in the presence of a base; ii. reacting the product from (i) with an enantiomerically pure acid (e.g., (-)-di-p-toluoyltartaric acid); iii. hydrolysis of the resulting intermediate, and iv. methylation and recovery of escitalopram (I). The current process minimizes the production of undesired byproducts.

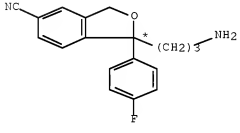
RX(1) OF 27 A + B ===> C...



A

B

(1)



C

RX(1) RCT A 64169-67-1

STAGE(1)
RGT D 865-47-4 t-BuOK
SOL 67-68-5 DMSO
CON SUBSTAGE(1) 60 - 65 deg C
SUBSTAGE(2) 10 minutes, 25 - 30 deg C
SUBSTAGE(3) 15 - 20 minutes, 25 - 30 deg C

STAGE(2)
RCT B 14753-26-5
SOL 67-68-5 DMSO
CON SUBSTAGE(1) 25 - 30 deg C
SUBSTAGE(2) 60 - 70 minutes, 30 deg C -> 45 deg C

STAGE(3)
RGT E 7732-18-5 Water
CON cooled

STAGE(4)

```
              RGT  F 7647-01-0 HCl
              SOL  7732-18-5 Water
              CON  pH 2 - 3

            STAGE(5)
              RGT  G 1310-73-2 NaOH
              SOL  7732-18-5 Water
              CON  pH 10 - 11

          PRO  C 62498-69-5
          NTE  regioselective in stage 2, acetone can also be used as
               solvent
REFERENCE COUNT:          1     THERE ARE 1 CITED REFERENCES AVAILABLE FOR
                                THIS RECORD. ALL CITATIONS AVAILABLE IN THE
                                RE FORMAT

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L54          109 S ("MATHAD V"? OR "VIJAYAVITHAI M"?)/AU
L55            2 S ("VENKAVALA P"? OR "PRAVINACHANDRA V"?)/AU
L56           42 S ("ELATI C"? OR "CHANDRASHEKAR E"?)/AU
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L58         1008 S ("GOVINDAN S"? OR "SHANMUGAM G"?)/AU
L59           13 S ("CHALAMALA S"? OR "SUBRAHMANYESHWARA C"?)/AU
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L61           21 S L53 AND (L54-L59)
L62           53 S L54 AND (L55-L59)
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L67            8 S (L53-L58 OR L61 OR L62 OR L64 OR L65) AND L47
L68            8 S L60 OR L63 OR L66 OR L67
L69            7 DUP REM L68 (1 DUPLICATE REMOVED)

L69  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2009:209477  CAPLUS  Full-text
TITLE:                    Composition of escitalopram oxalate
                          powders
INVENTOR(S):              Kolla, Naveen Kumar; Elati, Ravi Ram;
                          Gangula, Srinivas
PATENT ASSIGNEE(S):       India
SOURCE:                   U.S. Pat. Appl. Publ., 5pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
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     US 20090048336       A1    20090219    US 2008-193201           20080818
PRIORITY APPLN. INFO.:                      IN 2007-CH1835      A    20070817

                                            US 2008-39159P      P    20080325

AB   The present invention relates to escitalopram oxalate powders having definite
     particle size distribution parameters, processes for preparing the powders,
     and solid pharmaceutical formulations containing the powders.  Specifically,
```

the processes for manufacturing escitalopram oxalate powders comprises: (1) providing a solution of escitalopram in an organic solvent; (2) reacting with oxalic acid to produce escitalopram oxalate and cause its precipitation as a solid; (3) isolating the solid; and (4) micronizing the solid to obtain escitalopram oxalate having defined particle size parameters.

L69 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1411318 CAPLUS Full-text
DOCUMENT NUMBER: 150:55901
TITLE: Substrate Modification Approach to Achieve Efficient Resolution: Didesmethylcitalopram: A Key Intermediate for Escitalopram. Response to comments
AUTHOR(S): Elati, Chandrashekar R.; Kolla, Naveenkumar; Mathad, Vijayavitthal T.
CORPORATE SOURCE: Department of Research and Development, Dr. Reddy's Laboratories Ltd., Hyderabad, Andhrapradesh, 502325, India
SOURCE: Organic Process Research & Development (2009), 13(1), 34-37
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
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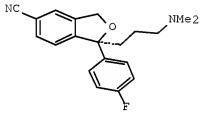

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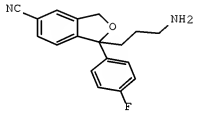

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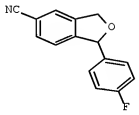

III

AB Recently, we published a synthesis of (S)-escitalopram (I) consisting of the resolution of didesmethylcitalopram (II) and subsequent methylation of S-didesmethylcitalopram. Some of our observations regarding citalopram resolution and C-alkylation of a benzofuran analog III to produce didesmethylcitalopram (II) were disputed by Dr. Dancer of H. Lundbeck (preceding article). A detailed response to his comments regarding stabilization of the 3-chloropropylamine free base by dilution with certain solvents, its storage and handling, optimized exptl. conditions for C-

alkylation to prepare didesmethylcitalopram, and a corrected process for citalopram resolution are included.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:691100 CAPLUS Full-text
DOCUMENT NUMBER: 147:234934
TITLE: Substrate modification approach to achieve efficient resolution: didesmethylcitalopram: a key intermediate for escitalopram. [Erratum to document cited in CA146:316708]
AUTHOR(S): Elati, Chandrashekar R.; Kolla, Naveenkumar; Vankawala, Pravinchandra J.; Gangula, Srinivas; Chalamala, Subrahmanyeswarara; Sundaram, Venkatraman; Bhattacharya, Apurba; Vurimidi, Himabindu; Mathad, Vijayavitthal T.
CORPORATE SOURCE: Department of Research and Development, Dr. Reddy's Laboratories Ltd., Hyderabad, 502325, India
SOURCE: Organic Process Research & Development (2007), 11(4), 780
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB On page 292, in last paragraph, the correct exptl. details should read: "S-(=)-1-(3-Dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3- dihydro-isobenzofuran-5-carbonitrile (s-(+)-1•(-)-DPTTA). A mixture of compound 1a (25 g. 0.077 mol) and acetonitrile (125 mL) was stirred at room temperature for 5 min, and then a solution of (-) DPTTA monohydrate (31.4 g, 0.077 mol) in acetonitrile (125 mL) was added and the mixture stirred for 10-15 min. To the resultant white precipitate was added methanol (20 mL) slowly at 70-75°, and the resulting clear solution was slowly cooled to room temperature After cooling the flask to 0-5° for 1.0-1.5 h, the resulting solid was filtered. The recrystn. with acetonitrile/methanol was repeated for two more times, and the resulting solid was filtered. The filtered cake was washed with acetonitrile (20 mL) and dried at 60-65° to afford 9.8 g of 1·(-)-DPTTA. Yield (%): 36 (calculated relative to theor. which is half of the starting racemate). The DPTTA salt was hydrolyzed to afford escitalopram free base (1). [α]D for free base = 10.8 (c 1, methanol); chiral purity: 98.4%, H NMR for free base (200 MHz, DMSO-d6): 1.18-1.28 (m, 2H), 2.01 (s, 6H), 2.11-2.18 (m,4H), 5.11-5.20 (q,J=13.2 and 11.2 Hz, 2H), 7.12-7.16 (t, J + 8.8Hz, 2H), 7.56-7.59 (dd, j+5.2 and 3.6 Hz, 2H), 7.73-7.78 (m, 3H); MS (APCI) m/z 325 (M+ = 1).".

L69 ANSWER 4 OF 7 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2007495262 EMBASE Full-text
TITLE: Psychiatric Considerations in Pulmonary Disease.
AUTHOR: Shanmugam, Ganesh; Bhutani, Sumit; Khan, David A.
CORPORATE SOURCE: Division of Allergy and Immunology, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8849, United States.
AUTHOR: Brown, E. Sherwood, Dr. (correspondence)
CORPORATE SOURCE: Department of Psychiatry, University of Texas

Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8849, United States. sherwood.brown@utsouthwestern.edu
SOURCE: Psychiatric Clinics of North America, (Dec 2007) Vol. 30, No. 4, pp. 761-780.
Refs: 92
ISSN: 0193-953X CODEN: PCAMDG
PUBLISHER IDENT.: S 0193-953X(07)00078-0
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Oct 2007
Last Updated on STN: 30 Oct 2007
AB Lung disease is a prominent cause of morbidity and mortality worldwide. When a patient has a common lung disease, such as asthma, or a less prevalent one, such as idiopathic pulmonary fibrosis, psychiatric issues should be considered as an integral part of the care plan for each patient. There have been many studies of psychologic factors and psychiatric syndromes in various lung diseases and their treatment. In this article, the authors focus on an evidence-based approach to reviewing this clinical literature. .COPYRGT. 2007 Elsevier Inc. All rights reserved.

L69 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:52599 CAPLUS Full-text
DOCUMENT NUMBER: 146:316708
TITLE: Substrate Modification Approach to Achieve Efficient Resolution: Didesmethylcitalopram: A Key Intermediate for Escitalopram
AUTHOR(S): Elati, Chandrashekar R.; Kolla, Naveenkumar; Vankawala, Pravinchandra J.; Gangula, Srinivas; Chalamala, Subrahmanyeswarara; Sundaram, Venkatraman; Bhattacharya, Apurba; Vurimidi, Himabindu; Mathad, Vijayavitthal T.
CORPORATE SOURCE: Department of Research and Development, Dr. Reddy's Laboratories Ltd., Hyderabad, 502325, India
SOURCE: Organic Process Research & Development (2007), 11(2), 289-292
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:316708
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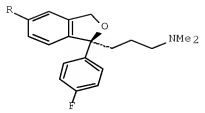

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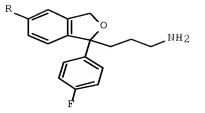

II

AB An approach to achieve the enantiopure escitalopram I (R = CN or Br) via didesmethyl escitalopram II, which is easily resolvable compared to citalopram I (R = CN) through diastereomeric salt crystallization was reported. The resolved intermediate (didesmethylcitalopram) was subsequently used for the preparation of the desired drug. This simple modification of the substrate makes a remarkable difference in the chemical resolution process. The first resolution of didesmethylcitalopram (±)-II to furnish (+)-II, a novel key intermediate to assemble escitalopram I (R = CN) was achieved via diastereomeric salt resolution using (-)-di-p-toluoyltartaric acid (DPTTA). The resolution conditions were optimized; a key feature of this process is the addition of specific quantity of water at a specific temperature to the reaction mixture

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L69 ANSWER 6 OF 7 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2006555521 EMBASE Full-text
TITLE: Zolmitriptan nasal spray in the treatment of migraine.
AUTHOR: Govindan, Srini, Dr. (correspondence)
CORPORATE SOURCE: 40 Medical Park, Wheeling, WV 26003, United States.
GovindanA@cs.com
SOURCE: Thermology International, (Oct 2006) Vol. 16, No. 4, pp. 132-137.
Refs: 27
ISSN: 1560-604X CODEN: TIHNAZ
COUNTRY: Austria
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English; German
ENTRY DATE: Entered STN: 28 Nov 2006
Last Updated on STN: 28 Nov 2006

AB Migraine patients have both intra and extra cranial vasomotor abnormalities. In migraine there are associated changes in neuropeptides eg., CGRP and it's effects on the trigeminovascular system. Infrared Imaging of Extracranial/Facial bloodflow and vasomotor response with induced hyperoxia before and after treatment with Zomig® (Zolmitriptan) Nasal Spray, a drug approved in the treatment of acute migraine was done in this case. In migraine vasomotor abnormalities are imaged as asymmetrical perfusion/facial temperature pattern by thermography. Subjecting the patient to vasomotor and pharmacological challenges during migraine can help us to understand the pathophysiology.

L69 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2005:451372 CAPLUS Full-text
DOCUMENT NUMBER: 142:481937
TITLE: Preparation of enantiomerically enriched escitalopram
INVENTOR(S): Sundaram, Venkataraman; Mathad, Vijayavitthal Thippannachar; Venkavala, Pravinachandra Jayanthilal; Elati, Chandrashekar Ravirama; Kolla, Naveenkumar; Govindan, Shanmugam; Chalamala, Subrahmanyeshwara Rao; Gangula, Srinivas
PATENT ASSIGNEE(S): Reddy's Laboratories, Inc., USA; Reddy's Laboratories Ltd.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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CA 2575975	A1	20050526	CA 2004-2575975	20041112
EP 1706394	A1	20061004	EP 2004-811264	20041112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
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US 20090018351	A1	20090115	US 2007-595794	20070130
PRIORITY APPLN. INFO.:			IN 2003-CH924 A	20031112
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			WO 2004-US38490 W	20041112

OTHER SOURCE(S): CASREACT 142:481937
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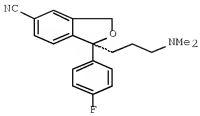

I

AB A process is disclosed for the preparation of enantiomerically enriched escitalopram. The process is comprised of: i. reacting 5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran with 3-chloropropylamine in the presence of a base; ii. reacting the product from (i) with an enantiomerically pure acid (e.g., (-)-di-p-toluoyltartaric acid); iii. hydrolysis of the resulting intermediate, and iv. methylation and recovery of escitalopram (I). The current process minimizes the production of undesired byproducts.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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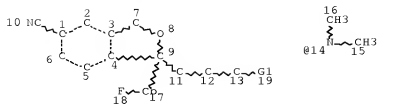

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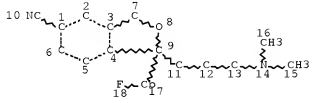

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STEREO ATTRIBUTES: NONE
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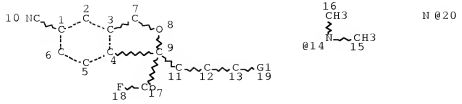

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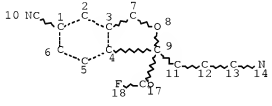

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DEFAULT ECLEVEL IS LIMITED

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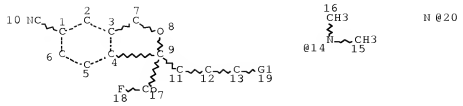
L25 15 SEA FILE=REGISTRY SUB=L23 SSS FUL L24

L12 STR



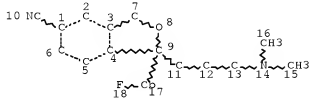
VAR G1=14/20
NODE ATTRIBUTES:
CONNECT IS X2 RC AT 11
CONNECT IS X2 RC AT 12
CONNECT IS X2 RC AT 13
CONNECT IS X1 RC AT 20
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 17
GGCAT IS MCY UNS AT 17
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

L14 20 SEA FILE=MARPAT SSS FUL L12 (MODIFIED ATTRIBUTES)
L15 STR



NODE ATTRIBUTES:
CONNECT IS X2 RC AT 2
CONNECT IS X2 RC AT 5
CONNECT IS X2 RC AT 6
CONNECT IS X2 RC AT 7
CONNECT IS X3 RC AT 14
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 17
GGCAT IS UNS AT 17
DEFAULT ECLEVEL IS LIMITED

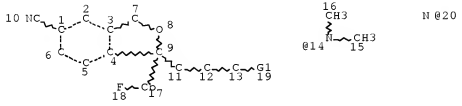
GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

L17 18 SEA FILE=MARPAT SUB=L14 SSS FUL L15 (MODIFIED ATTRIBUTES)

L12 STR



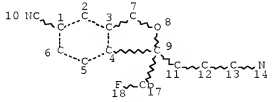
VAR G1=14/20
NODE ATTRIBUTES:
CONNECT IS X2 RC AT 11
CONNECT IS X2 RC AT 12
CONNECT IS X2 RC AT 13
CONNECT IS X1 RC AT 20
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 17
GGCAT IS MCY UNS AT 17
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

L14 20 SEA FILE=MARPAT SSS FUL L12 (MODIFIED ATTRIBUTES)
L38 STR



NODE ATTRIBUTES:
CONNECT IS X2 RC AT 2
CONNECT IS X2 RC AT 5
CONNECT IS X2 RC AT 6
CONNECT IS X2 RC AT 7
CONNECT IS X1 RC AT 14

```
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  17
GGCAT   IS UNS  AT  17
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  16

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

L39           9 SEA FILE=MARPAT SUB=L14 SSS FUL L38 (MODIFIED ATTRIBUTES)

     FILE 'REGISTRY' ENTERED AT 16:02:46 ON 05 MAR 2009
                ACT R595B/A
                ---------
L1              STR
L2  (       125)SEA SSS FUL L1
L3              STR
L4           97 SEA SUB=L2 SSS FUL L3
               ---------
                D QUE
L5            3 SEA ABB=ON  PLU=ON  (3-CHLOROPROPYLAMINE/CN OR "3-CHLOROPRO
                PYLAMINE HYDROCHLORIDE"/CN OR "3-CHLOROPROPYLAMINE-1-13C
                HYDROCHLORIDE"/CN)

     FILE 'CAPLUS' ENTERED AT 16:19:20 ON 05 MAR 2009
L6          461 SEA ABB=ON  PLU=ON  L5 OR 3(W)(CHLOROPROPYLAMINE OR (CL OR
                CHLORO)(W)(PROPYLAMINE OR (PROPYL OR PR)(W)AMINE) OR
                CHLOROPROPYL AMINE OR AMINOPROPYLCHLORIDE OR (AMINOPROPYL
                OR AMINO(W)(PR OR PROPYL))(W)(CL OR CHLORIDE))
L7          165 SEA ABB=ON  PLU=ON  L4/P
L8            6 SEA ABB=ON  PLU=ON  L6 AND L7
                SEL HIT L8 1-6 RN
                D 1-6 IBIB ABS HITSTR

     FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 16:23:08 ON 05 MAR 2009
L9        16863 SEA ABB=ON  PLU=ON  L4
L10           5 SEA ABB=ON  PLU=ON  L9(L)(PREP? OR MANUF? OR PRODUCTION OR
                PRODUCING OR PRODUCE#)
L11           2 DUP REM L10 (3 DUPLICATES REMOVED)
                D 1-2 IBIB ABS

     FILE 'MARPAT' ENTERED AT 16:24:27 ON 05 MAR 2009
L12             STR L1
L13           0 SEA SSS SAM L12 (MODIFIED ATTRIBUTES)
L14          20 SEA SSS FUL L12 (MODIFIED ATTRIBUTES)
                D QUE STAT
L15             STR L3
L16           0 SEA SSS SAM L15 (MODIFIED ATTRIBUTES)
L17          18 SEA SUB=L14 SSS FUL L15 (MODIFIED ATTRIBUTES)
                D QUE STAT

     FILE 'CAPLUS' ENTERED AT 16:26:15 ON 05 MAR 2009
L18          18 SEA ABB=ON  PLU=ON  L17
L19           0 SEA ABB=ON  PLU=ON  L18 AND L6
```

```
L20          16 SEA ABB=ON  PLU=ON  L18 AND (PREP OR BMF OR IMF OR SPN OR
                BPN)/RL

     FILE 'MARPAT' ENTERED AT 16:28:08 ON 05 MAR 2009
L21          16 SEA ABB=ON  PLU=ON  L20
                D 1-16

     FILE 'REGISTRY' ENTERED AT 16:28:37 ON 05 MAR 2009
                D SAV
                ACT R595C/A
                ---------
L22             STR
L23 (       125)SEA SSS FUL L22
L24             STR
L25          15 SEA SUB=L23 SSS FUL L24
                ---------
                D QUE STAT

     FILE 'CAPLUS' ENTERED AT 16:29:05 ON 05 MAR 2009
L26          82 SEA ABB=ON  PLU=ON  L25
L27           7 SEA ABB=ON  PLU=ON  L26(L)(OPTIAL? OR CHIRAL OR ENRIOMER?
                OR RESOLUT? OR METHYLAT?)
L28          11 SEA ABB=ON  PLU=ON  L26(L)(RACT OR RCT)/RL
L29          15 SEA ABB=ON  PLU=ON  L27 OR L28
L30          12 SEA ABB=ON  PLU=ON  L29 NOT (L8 OR L20)
                SEL HIT L30 1-12 RN
                D 1-12 IBIB ABS HITSTR

     FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 16:36:47 ON 05 MAR 2009
L31          63 SEA ABB=ON  PLU=ON  L25
L32           0 SEA ABB=ON  PLU=ON  L31(L)(OPTIAL? OR CHIRAL OR ENRIOMER?
                OR RESOLUT? OR METHYLAT?)
L33           0 SEA ABB=ON  PLU=ON  L31(L)(REACT? OR REAGENT OR RXN)
L34          12 SEA ABB=ON  PLU=ON  L31 AND (REACT? OR REAGENT OR RXN)
L35          10 SEA ABB=ON  PLU=ON  L31 AND (OPTIAL? OR CHIRAL OR ENRIOMER?
                 OR RESOLUT? OR METHYLAT?)
L36          19 SEA ABB=ON  PLU=ON  L34 OR L35
L37          18 DUP REM L36 (1 DUPLICATE REMOVED)
                D 1-18 IBIB ABS

     FILE 'MARPAT' ENTERED AT 16:38:14 ON 05 MAR 2009
                D L15
                D L14
                D QUE L14
L38             STR L24
L39           9 SEA SUB=L14 SSS FUL L38 (MODIFIED ATTRIBUTES)
                D QUE STAT

     FILE 'CAPLUS' ENTERED AT 16:40:15 ON 05 MAR 2009
L40           9 SEA ABB=ON  PLU=ON  L39
L41           2 SEA ABB=ON  PLU=ON  L40 NOT (L8 OR L20 OR L30)
L42           0 SEA ABB=ON  PLU=ON  L41 AND (OPTIAL? OR CHIRAL OR ENRIOMER?
                 OR RESOLUT? OR METHYLAT?)
L43           2 SEA ABB=ON  PLU=ON  L41 AND (RACT OR RCT)/RL

     FILE 'MARPAT' ENTERED AT 16:41:04 ON 05 MAR 2009
L44           2 SEA ABB=ON  PLU=ON  L43
L45           2 SEA ABB=ON  PLU=ON  L44 NOT L21
                D 1-2 IBIB ABS
```

```
     FILE 'REGISTRY' ENTERED AT 16:42:16 ON 05 MAR 2009
                  E ESCITALOPRAM/CN 5
L46             2 SEA ABB=ON  PLU=ON  (ESCITALOPRAM/CN OR "ESCITALOPRAM
                  OXALATE"/CN)
                  D CN 1-2

     FILE 'CAPLUS' ENTERED AT 16:42:44 ON 05 MAR 2009
L47          3512 SEA ABB=ON  PLU=ON  L46 OR ESCITALOPRAM OR CITALOPRAM OR
                  LEXAPRO
L48             5 SEA ABB=ON  PLU=ON  L47 AND L6
L49             1 SEA ABB=ON  PLU=ON  L48 NOT (L8 OR L20 OR L30 OR L43)
                  D

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS' ENTERED
     AT 16:44:20 ON 05 MAR 2009
L50             1 SEA ABB=ON  PLU=ON  L48
                  D IBIB ABS

     FILE 'CASREACT' ENTERED AT 16:45:03 ON 05 MAR 2009
L51            22 SEA ABB=ON  PLU=ON  L46/PRO
L52             1 SEA ABB=ON  PLU=ON  L51 AND L5
                  D IBIB ABS FHIT

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS'
     ENTERED AT 16:45:47 ON 05 MAR 2009
L53          2000 SEA ABB=ON  PLU=ON  ("SUNDARAM V"? OR "VENKATARAMAN
                  S"?)/AU
L54           109 SEA ABB=ON  PLU=ON  ("MATHAD V"? OR "VIJAYAVITHAI M"?)/AU
L55             2 SEA ABB=ON  PLU=ON  ("VENKAVALA P"? OR "PRAVINACHANDRA
                  V"?)/AU
L56            42 SEA ABB=ON  PLU=ON  ("ELATI C"? OR "CHANDRASHEKAR E"?)/AU
L57            51 SEA ABB=ON  PLU=ON  ("KOLLA N"? OR "NAVEENKUMAR K"?)/AU
L58          1008 SEA ABB=ON  PLU=ON  ("GOVINDAN S"? OR "SHANMUGAM G"?)/AU
L59            13 SEA ABB=ON  PLU=ON  ("CHALAMALA S"? OR "SUBRAHMANYESHWARA
                  C"?)/AU
L60             2 SEA ABB=ON  PLU=ON  L53 AND L54 AND L55 AND L56 AND L57
                  AND L58 AND L59
L61            21 SEA ABB=ON  PLU=ON  L53 AND ((L54 OR L55 OR L56 OR L57 OR
                  L58 OR L59))
L62            53 SEA ABB=ON  PLU=ON  L54 AND ((L55 OR L56 OR L57 OR L58 OR
                  L59))
L63             2 SEA ABB=ON  PLU=ON  L55 AND ((L56 OR L57 OR L58 OR L59))
L64            21 SEA ABB=ON  PLU=ON  L56 AND ((L57 OR L58 OR L59))
L65            11 SEA ABB=ON  PLU=ON  L57 AND (L58 OR L59)
L66             2 SEA ABB=ON  PLU=ON  L58 AND L59
L67             8 SEA ABB=ON  PLU=ON  ((L53 OR L54 OR L55 OR L56 OR L57 OR
                  L58) OR L61 OR L62 OR L64 OR L65) AND L47
L68             8 SEA ABB=ON  PLU=ON  L60 OR L63 OR L66 OR L67
L69             7 DUP REM L68 (1 DUPLICATE REMOVED)
                  D 1-7 IBIB ABS

     FILE 'HOME' ENTERED AT 16:50:26 ON 05 MAR 2009
                  D QUE L4
                  D QUE L25
                  D QUE L17
                  D QUE L39


     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
```

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STRUCTURE FILE UPDATES: 4 MAR 2009 HIGHEST RN 1115640-24-8
DICTIONARY FILE UPDATES: 4 MAR 2009 HIGHEST RN 1115640-24-8

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http://www.cas.org/support/stngen/stndoc/properties.html

FILE CAPLUS

FILE COVERS 1907 - 5 Mar 2009 VOL 150 ISS 10
FILE LAST UPDATED: 4 Mar 2009 (20090304/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2008.

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FILE WPIX
FILE LAST UPDATED: 27 FEB 2009 <20090227/UP>
MOST RECENT UPDATE: 200913 <200913/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE
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>>> IPC and US National Classifications have been updated with reclassifications to the end of 2008. ECLA classifications are complete to the end of 2008 and F-Term and FI-Term classifications to the end of 2007. No update date (UP) has been created for the reclassified documents, but they can be identified by specific update codes (see HELP CLA for details)<<<

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>>> HELP for European Patent Classifications see HELP ECLA, HELP ICO <

FILE HOME

FILE MEDLINE
FILE LAST UPDATED: 4 Mar 2009 (20090304/UP). FILE COVERS 1949 TO DAT

MEDLINE and LMEDLINE have been updated with the 2009 Medical Subject Headings (MeSH) vocabulary and tree numbers from the U.S. National L of Medicine (NLM). Additional information is available at

http://www.nlm.nih.gov/pubs/techbull/nd08/nd08_medline_data_changes_2

On February 21, 2009, MEDLINE was reloaded. See HELP RLOAD for detai

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See HELP RANGE before carrying out any RANGE search.

FILE BIOSIS
FILE COVERS 1926 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1926 TO DATE.

RECORDS LAST ADDED: 4 March 2009 (20090304/ED)

BIOSIS has been augmented with 1.8 million archival records from 1926 through 1968. These records have been re-indexed to match current BIOSIS indexing.

FILE EMBASE
FILE COVERS 1974 TO 5 Mar 2009 (20090305/ED)

EMBASE was reloaded on March 30, 2008.

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

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Beginning January 2008, Elsevier will no longer provide EMTREE codes as part of the EMTREE thesaurus in EMBASE. Please update your current-awareness alerts (SDIs) if they contain EMTREE codes.

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FILE MARPAT

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FILE CONTENT: 1961-PRESENT VOL 150 ISS 8 (20090227/ED)

MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US  20090018200 15 JAN 2009
DE 102007040251 08 JAN 2009
EP      2014745 14 JAN 2009
JP   2009007348 15 JAN 2009
WO   2009012656 29 JAN 2009
GB      2450771 07 JAN 2009
FR      2918372 09 JAN 2009
RU      2342397 27 DEC 2008
CA      2631186 19 DEC 2008

Expanded G-group definition display now available.

The new MARPAT User Guide is now available at:
 http://www.cas.org/support/stngen/stndoc/marpat.html.

FILE JAPIO
FILE LAST UPDATED:            25 FEB 2009       <20090225/UP>
MOST RECENT PUBLICATION DATE: 27 NOV 2008       <20081127/PD>

>>> GRAPHIC IMAGES AVAILABLE <<<

FILE PASCAL
FILE LAST UPDATED: 2 MAR 2009       <20090302/UP>
FILE COVERS 1977 TO DATE.

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FILE COVERS 1861 TO 25 FEB 2009 (20090225/ED)

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FILE CONTENT:1840 - 2 Mar 2009 VOL 150 ISS 10

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**************************************************
*                                                *
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